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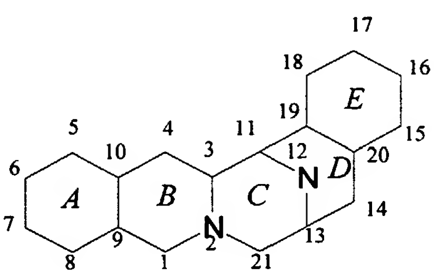
(54) Title: ANTITUMORAL ANALOGS OF ET-743



(XIV)

(57) Abstract: Antitumour compounds have the five membered fused ring ecteinascidin structure of the formula (XIV). The present compounds lack a 1,4-bridging group as found in the ecteinascidins. They have at the C-1 position a substituent selected from an optionally protected or derivatised aminomethylene group or an optionally protected or derivatised hydroxymethylene group.

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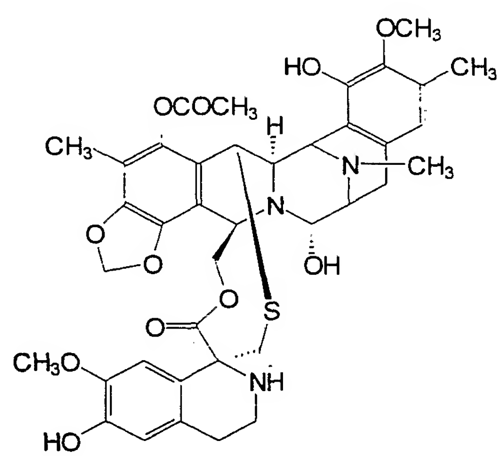
ANTITUMORAL ANALOGS OF ET-743

The present invention relates to antitumoral compounds, and in particular to antitumoral analogs of ecteinascidin 743, ET-743.

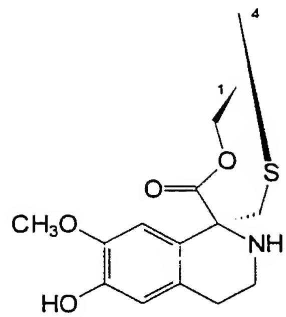
BACKGROUND OF THE INVENTION

European Patent 309,477 relates to ecteinascidins 729, 743, 745, 759A, 759B and 770. The ecteinascidin compounds are disclosed to have antibacterial and other useful properties. Ecteinascidin 743 is now undergoing clinical trials as an antitumour agent.

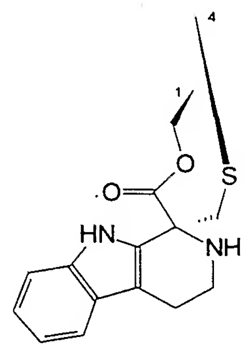
Ecteinascidin 743 has a complex tris(tetrahydroisoquinolinephenol) structure of the following formula (I):



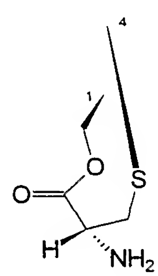
In ecteinascidin 743, the 1,4 bridge has the structure of formula (IV):



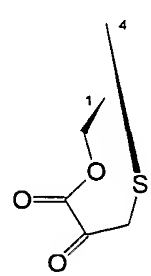
Other known ecteinascidins include compounds with a different bridged cyclic ring system, such as occurs in ecteinascidin 722 and 736, where the bridge has the structure of formula (V):



ecteinascidins 583 and 597, where the bridge has the structure of formula (VI):



and ecteinascidin 594 and 596, where the bridge has the structure of formula (VII):



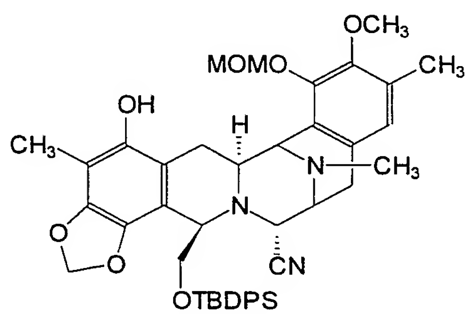
The complete structure for these and related compounds is given in J. Am. Chem.

Soc. (1996) 118, 9017-9023. This article is incorporated by reference.

The ecteinascidins are currently prepared by isolation from extracts of the marine tunicate *Ecteinascidin turbinata*. The yield is low, and alternative preparative processes have been sought.

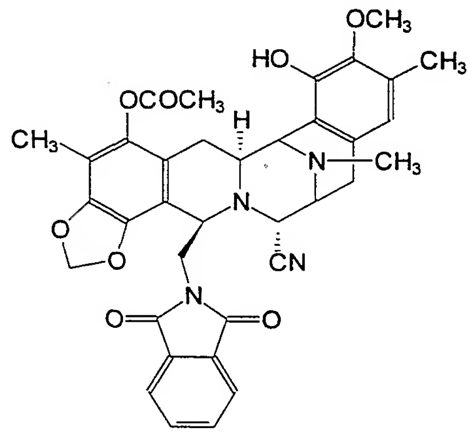
A synthetic process for producing ecteinascidin compounds is described in US Patent 5,721,362, see also WO 9812198. The claimed method is long and complicated. By way of illustration, there are 38 Examples each describing one or more steps in the synthetic sequence to arrive at ecteinascidin 743.

Claim 25 of US 5,721,362 is directed at an intermediate phenol compound of a given formula (11), which we refer to also as Intermediate 11 or Int-11. It has the following bis(tetrahydroisoquinolinephenol) structure (II):

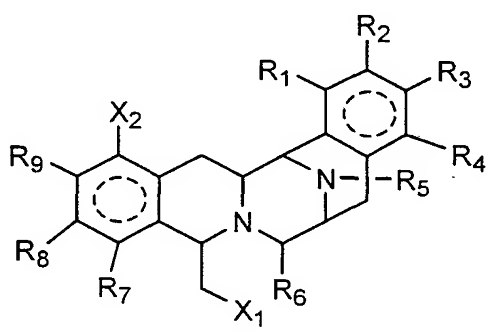


where MOM is a methoxymethyl substituent and TBDPS is a tert-butyldiphenylsilyl substituent.

From Intermediate 11 it is possible to synthesise another interesting antitumour agent, phthalascidin, see Proc. Natl. Acad. Sci. USA, 96, 3496-3501, 1999. Phthalascidin is a bis(tetrahydroisoquinolinephenol) derivative of formula (III):



More generally, phthalascidin and related compounds are described in WO 0018233. Claim 1 is directed at compounds of formula:



wherein the substituent groups defined by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are each independently selected from the group consisting of H, OH, OR′, SH, SR′, SOR′, SO_2R', NO_2, NH_2, NHR′, $N(R')_2$, NHC(O)R′, CN, halogen,=O, C(=O)H, C(=O)R′, CO_2H, CO_2R', C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, and substituted or unsubstituted heteroaromatic;

wherein each of the R′ groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, =O, C(=O)H, $C(=O)CH_3$, CO_2H, CO_2CH_3, C_1-C_{12} alkyl, C_2-C_{12} alkenyl, C_2-C_{12} alkynyl, aryl, aralkyl, and heteroaromatic;

wherein each dotted circle represents one, two or three optional double bonds;

wherein R_7 and R_8 may be joined into a carbocyclic or heterocyclic ring system;

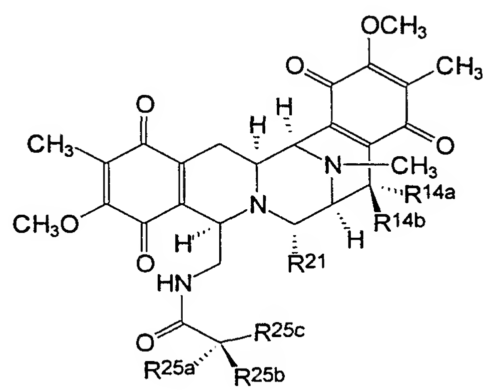
and wherein X_1 and X_2 are each independently defined as above for R_1-R_8 and further include various permitted definitions.

Further naturally occuring compounds are known which lack a bridged cyclic ring system. They include the bis(tetrahydroisoquinolinequinone) antitumor-antimicrobial antibiotics safracins and saframycins, and the marine natural products renieramicins and xestomycin isolated from cultured microbes or sponges. They all have a common dimeric tetrahydroisoquinoline carbon framework. These compounds can be classified into four types, types I to IV, with respect to the oxidation pattern of the aromatic rings.

Type I, dimeric isoquinolinequinones, is a system of formula (VIII) most commonly occurring in this class of compounds, see the following table I.

Table I

Structure of Type I Saframycin Antibiotics.

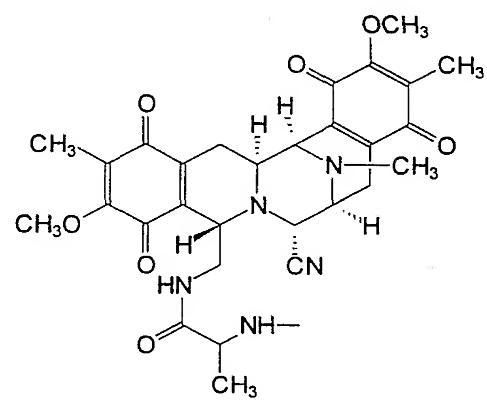


Compound	Substituents R^{14a}	R^{14b}	R^{21}	R^{25a}	R^{25b}	R^{25c}
saframycin A	H	H	CN	O	O	CH_3
saframycin B	H	H	H	O	O	CH_3
saframycin C	H	OCH_3	H	O	O	CH_3
saframycin G	H	OH	CN	O	O	CH_3
saframycin H	H	H	CN	OH	CH_2COCH_3	CH_3
saframycin S	H	H	OH	O	O	CH_3

saframycin Y_3	H	H	CN	NH_2	H	CH_3
saframycin Yd_1	H	H	CN	NH_2	H	C_2H_5
saframycin Ad_1	H	H	CN	O	O	C_2H_5
saframycin Yd_2	H	H	CN	NH_2	H	H
saframycin Y_{2b}	H	Q^b	CN	NH_2	H	CH_3
saframycin $Y_{2b\text{-}d}$	H	Q^b	CN	NH_2	H	C_2H_5
saframycin AH_2	H	H	CN	H^a	OH^a	CH_3
saframycin AH_2Ac	H	H	CN	H	OAc	CH_3
saframycin AH_1	H	H	CN	OH^a	H^a	CH_3
saframycin AH_1Ac	H	H	CN	OAc	H	CH_3
saframycin AR_3	H	H	H	H	OH	CH_3

[a] assignments are interchangeable.

[b] where the group Q is of formula (IX):



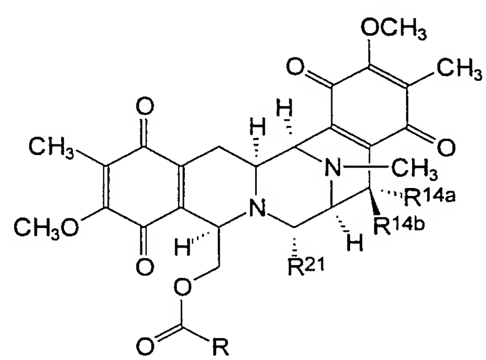
Type I aromatic rings are seen in saframycins A, B and C; G and H; and S isolated from *Streptomyces lavendulae* as minor components. A cyano derivative of saframycin A, called cyanoquinonamine, is known from Japanese Kokai JP-A2 59/225189 and 60/084288. Saframycins Y_3, Yd_1, Ad_1, and Yd_2 were produced by *S. lavendulae* by directed biosynthesis, with appropriate supplementation of the culture medium. Saframycins Y_{2b} and $Y_{2b\text{-}d}$ dimers formed by linking the nitrogen on the C-25 of one unit to the C-14 of the other, have also been produced in supplemented culture media of *S. lavendulae*. Saframycins AR_1 (=AH_2,), a microbial reduction product of saframycin A at C-25 produced by *Rhodococcus amidophilus*, is also prepared by nonstereoselective chemical reduction of saframycin A by sodium borohydride as a 1:1 mixture of epimers followed by chromatographic separation

[the other isomer AH_1 is less polar]. The further reduction product saframycin AR_3, 21-decyano-25-dihydro-saframycin A, (= 25-dihydrosaframycin B) was produced by the same microbial conversion. Another type of microbial conversion of saframycin A using a *Nocardia* species produced saframycin B and further reduction by a *Mycobacterium* species produced saframycin AH^1Ac. The 25-*O*-acetates of saframycin AH_2 and AH_1 have also been prepared chemically for biological studies.

Type I compounds of formula (X) have also been isolated from marines sponges, see Table II.

Table II

Structures of Type I Compounds from Marine Sponges.



	Substituents			
	R^{14a}	R^{14b}	R^{21}	R
renieramycin A	OH	H	H	$-C(CH_3)=CH-CH_3$
renieramycin B	OC_2H_5	H	H	$-C(CH_3)=CH-CH_3$
renieramycin C	OH	O	O	$-C(CH_3)=CH-CH_3$
renieramycin D	OC_2H_5	O	O	$-C(CH_3)=CH-CH_3$
renieramycin E	H	H	OH	$-C(CH_3)=CH-CH_3$
renieramycin F	OCH_3	H	OH	$-C(CH_3)=CH-CH_3$
xestomycin	OCH_3	H	H	$-CH_3$

Renieramycins A-D were isolated from the antimicrobial extract of a sponge, a *Reniera* species collected in Mexico, along with the biogenetically related monomeric isoquinolines renierone and related compounds. The structure of renieramycin A was

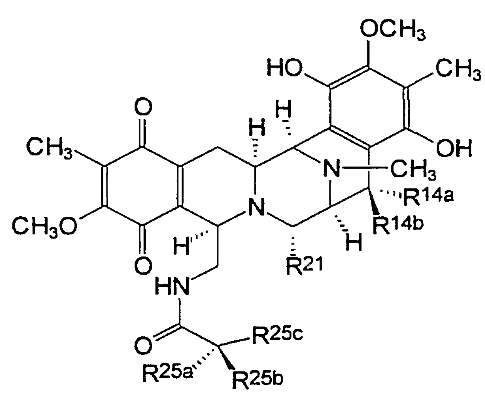
initially assigned with inverted stereochemistry at C-3, C-11, and C-13. However, careful examination of the ^{1}H NMR data for new, related compounds renieramycins E and F, isolated from the same sponge collected in Palau, revealed that the ring junction of renieramycins was identical to that of saframycins. This result led to the conclusion that the formerly assigned stereochemistry of renieramycins A to D must be the same as that of saframycins.

Xestomycin was found in a sponge, a *Xestospongia* species collected from Sri Lancan waters.

Type II compounds of formula (XI) with a reduced hydroquinone ring include saframycins D and F, isolated from *S. lavendulae*, and saframycins Mx-1 and Mx-2, isolated from *Myxococcus xanthus*. See table III.

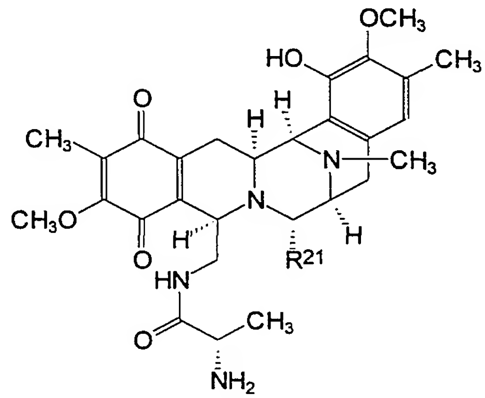
Table III

Type II Compounds



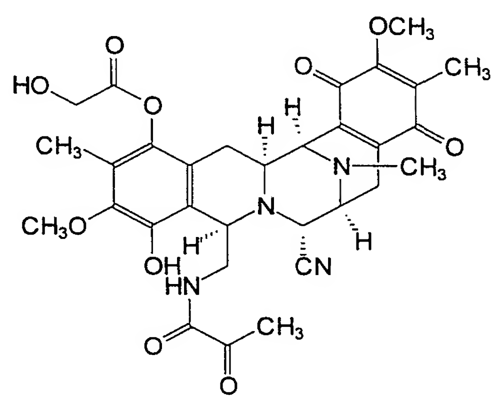
	Substituents					
Compound	R^{14a}	R^{14b}	R^{21}	R^{25a}	R^{25b}	R^{25c}
saframycin D	O	O	H	O	O	CH_3
saframycin F	O	O	CN	O	O	CH_3
saframycin Mx-1	H	OCH_3	OH	H	CH_3	NH_2
saframycin Mx-2	H	OCH_3	H	H	CH_3	NH_2

The type III skeleton is found in the antibiotics safracins A and B, isolated from cultured *Pseudomonas fluorescens*. These antibiotics of formula (XII) consist of a tetrahydroisoquinoline-quinone subunit and a tetrahydroisoqunínolinephenol subunit.

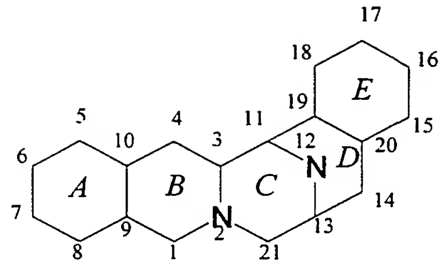


where R^{21} is -H in safracin A and is -OH in safracin B.

Saframycin R, the only compound classified as the Type IV skeleton, was also isolated from *S. lavendulae*. This compound of formula (XIII), consisting of a hydroquinone ring with a glycolic ester sidechain on one of the phenolic oxygens, is conceivably a pro-drug of saframycin A because of its moderate toxicity.



All these known compounds have a fused system of five rings (*A*) to (*E*) as shown in the following structure of formula (XIV):



The rings *A* and *E* are phenolic in the ecteinascidins and some other compounds, while in other compounds, notably the saframycins, the rings *A* and *E* are quinolic. In the known compounds, the rings *B* and *D* are tetrahydro, while ring *C* is perhydro.

Summary of the Invention

The present invention provides new compounds with the fused system of five rings (A) to (E). In particular, it provides new compounds which can be made from intermediates described in WO 9812198 or by a new process which is part of this invention. In this latter respect, we refer to our WO 0069862 published 23 November 2000, and which relates to hemisynthetic methods and new compounds. The present application claims priority from that PCT filing, and we incorporate that text by reference to the extent that there is disclosure therein which is not in the present specification.

In WO 0069862, various routes are described for the preparation of ecteinascidin compounds, including ecteinascidin 743, as well as ecteinascidin analogs including phthaliscidin. The present invention is founded partly on the use of intermediates of WO 0069862 to prepare further analogs of the ecteinasacidins.

Preferred Embodiments

We have found that compounds of the invention have exceptional activity in the treatment of cancers, such as leukaemias, lung cancer, colon cancer, kidney cancer and melanoma.

Thus, the present invention provides a method of treating any mammal, notably a human, affected by cancer which comprises administering to the affected individual a therapeutically effective amount of a compound of the invention, or a pharmaceutical composition thereof.

The present invention also relates to pharmaceutical preparations, which contain as active ingredient a compound or compounds of the invention, as well as the processes for their preparation.

Examples of pharmaceutical compositions include any solid (tablets, pills, capsules, granules, etc.) or liquid (solutions, suspensions or emulsions) with suitable composition or oral, topical or parenteral administration, and they may contain the pure compound or in combination with any carrier or other pharmacologically active compounds. These compositions may need to be sterile when administered parenterally.

Administration of the compounds or compositions of the present invention may be by any suitable method, such as intravenous infusion, oral preparations, intraperitoneal and intravenous administration. We prefer that infusion times of up to 24 hours are used, more preferably 2-12 hours, with 2-6 hours most preferred. Short infusion times which allow treatment to be carried out without an overnight stay in hospital are especially desirable. However, infusion may be 12 to 24 hours or even longer if required. Infusion may be carried out at suitable intervals of say 2 to 4 weeks. Pharmaceutical compositions containing compounds of the invention may be delivered by liposome or nanosphere encapsulation, in sustained release formulations or by other standard delivery means.

The correct dosage of the compounds will vary according to the particular formulation, the mode of application, and the particular *situs*, host and tumour being treated. Other factors like age, body weight, sex, diet, time of administration, rate of excretion, condition of the host, drug combinations, reaction sensitivities and severity of the disease shall be taken into account. Administration can be carried out continuously or periodically within the maximum tolerated dose.

The compounds and compositions of this invention may be used with other drugs to provide a combination therapy. The other drugs may form part of the same composition, or be provided as a separate composition for administration at the same time or a different time. The identity of the other drug is not particularly limited, and suitable candidates include:

a) drugs with antimitotic effects, especially those which target cytoskeletal elements, including microtubule modulators such as taxane drugs (such as taxol, paclitaxel, taxotere, docetaxel), podophylotoxins or vinca alkaloids (vincristine, vinblastine);

b) antimetabolite drugs such as 5-fluorouracil, cytarabine, gemcitabine, purine analogues such as pentostatin, methotrexate);

c) alkylating agents such as nitrogen mustards (such as cyclophosphamide or ifosphamide);

d) drugs which target DNA such as the antracycline drugs adriamycin, doxorubicin, pharmorubicin or epirubicin;

e) drugs which target topoisomerases such as etoposide;

f) hormones and hormone agonists or antagonists such as estrogens, antiestrogens (tamoxifen and related compounds) and androgens, flutamide, leuprorelin, goserelin, cyprotrone or octreotide;

g) drugs which target signal transduction in tumour cells including antibody derivatives such as herceptin;

h) alkylating drugs such as platinum drugs (cis-platin, carbonplatin, oxaliplatin, paraplatin) or nitrosoureas;

i) drugs potentially affecting metastasis of tumours such as matrix metalloproteinase inhibitors;

j) gene therapy and antisense agents;

k) antibody therapeutics;

l) other bioactive compounds of marine origin, notably the didemnins such as aplidine;

m) steroid analogues, in particular dexamethasone;

n) anti-inflammatory drugs, in particular dexamethasone;

o) anti-emetic drugs, in particular dexamethasone;

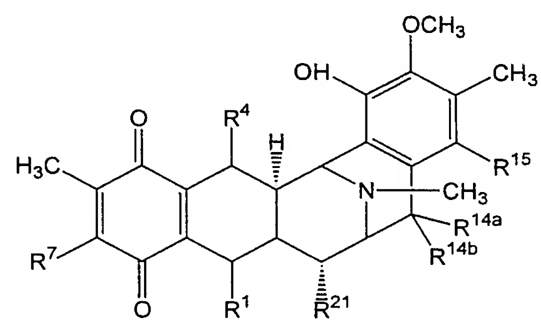
p) skeletal muscle protectors, such as L-carnitine or precursor amino acids.

The present invention also extends to the compounds of the invention for use in a method of treatment, and to the use of the compounds in the preparation of a composition for treatment of cancer.

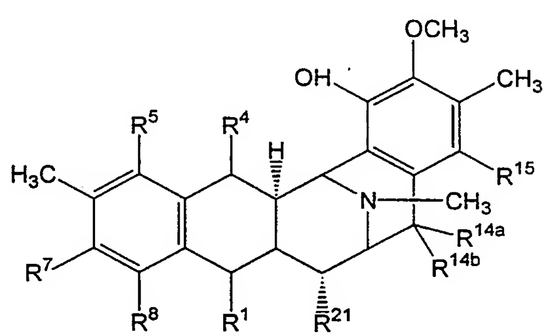
In one aspect of the invention, we make no claim to the compounds 2,3, 5, 8-OH-2, and 14 to 21 described in one or more of the GB priority patent applications for our PCT application published as 0069862. In a related aspect, the present invention extends to compounds which differ in respect of one or more of the substituents present at C-1, C-5, C-7, C-8, or C-18 in the compounds of these GB priority patent applications.

The compounds of this invention include compounds which do not have a hydroxy group at the C-18 position. Furthermore, the compounds of this invention include compounds which do not have a dicarboximidomethyl substituent, such as phthalimidomethyl, at the C-1 position. In particular, we provide active compounds where the subsituent X_1 is not as shown in the penultimate line at page 19 of WO0018233.

In one aspect, the analogs of this invention are typically of the formula (XVIIa):



or formula (XVIIb):



where

R^1 is an optionally protected or derivatised aminomethylene group, an optionally protected or derivatised hydroxymethylene group;

R^4 is -H;

R^5 is -H or -OH ;

R^7 is $-OCH_3$ and R^8 is -OH or R^7 and R^8 together form a group $-O-CH_2-O-$;

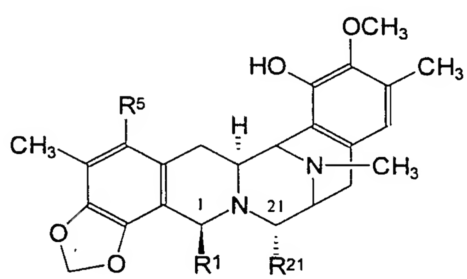
R^{14a} and R^{14b} are both -H or one is -H and the other is -OH, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group; and

R^{15} is -H or -OH;

R^{21} is -H, -OH or -CN;

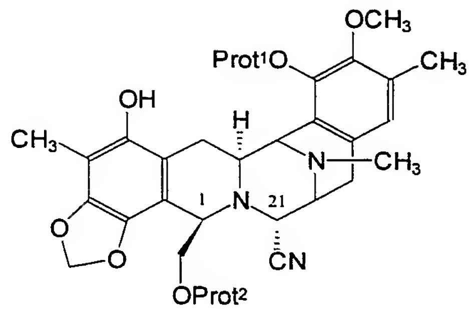
and derivatives including acyl derivatives thereof especially where R^5 is acetyloxy or other acyloxy group of up to 4 carbon atoms.

In the present invention, a key class of products includes phthalascidin and has the general formula (XX):



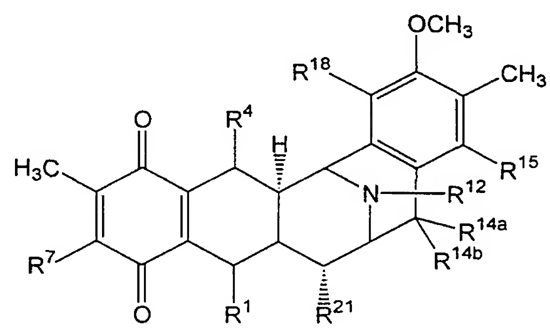
where R^1 is an amidomethylene group; R^5 is a small oxy-sidechain; and R^{21} is a cyano group or a hydroxy group. For phthalascidin, R^1 is a phthalimidomethylene group; R^5 an acetoxy group; and R^{21} is a cyano group. Other groups for R^1 include mono- and di-N-substituted amidomethylenes as well as other cyclic amidomethylenes, and other groups for R^5 include further C_1-C_4 acyl groups, as well as C_1-C_4 alkyl groups.

In the present invention, a key class of intermediates and analogs includes Intermediate 11 and has the general formula (XXI):

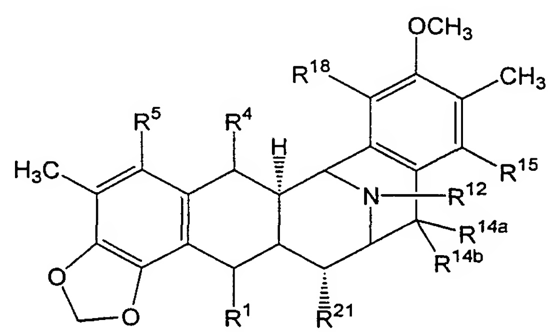


where $Prot^1$ and $Prot^2$ are hydroxy protecting groups, preferably different. For Intermediate 11 itself, the group $Prot^1$ is a methoxymethyl group, and $Prot^2$ is a t-butyldiphenylsilyl group.

In the light of the preceding explanations, it can be seen that the present invention provides novel analogs and novel intermediate compounds. Depending on ring A, the compounds include those of formula (XXIIa):



or of formula (XXIIb):



where:

R^1 is $-CH_2NH_2$ or $-CH_2OH$, or a protected or derivatised version of such a group and R^4 is -H;

R^5 is -OH or a protected or derivatised version of such a group;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH or a protected or derivatised version of such a group, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group;

R^{12} is -H-, $-CH_3$- or $-CH_2CH_3$-;

R^{15} is –H, -OH or a protected or derivatised version of such a group; and

R^{18} is -OH or a protected or derivatised version of such a group.

In one embodiment, preferably at least of R^1 , R^5, R^{14a}, R^{14b}, R^{15} or R^{18} is a protected or derivatised group.

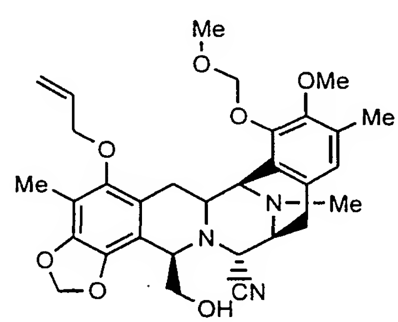
In one variation of this invention, the group R^1 is not a tert-butyldiphenylsilyl substituent and/or the group R^{18} is not a methoxymethyloxy group.

Preferably R^1 is $-CH_2NH_2$ or $-CH_2OH$, or a protected or derivatised version of such a group and R^4 is –H.

Preferably R^{14a} and R^{14b} are both -H.

Preferably R^{12} is $-CH_3$.

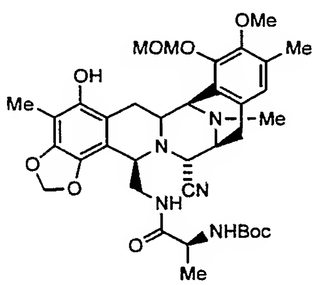
One preferred class of intermediates includes the compound which we identify as compound **25**, of formula:



25

The preferred class is thus of the general formula where the group MOM is replaced by any other protecting group, and/or the allyl is replaced by any other protecting group.

Other preferred intermediates includes the compounds which we identify as compounds **17, 43** and **45**.



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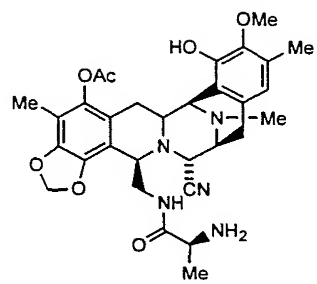

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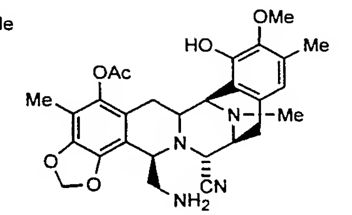
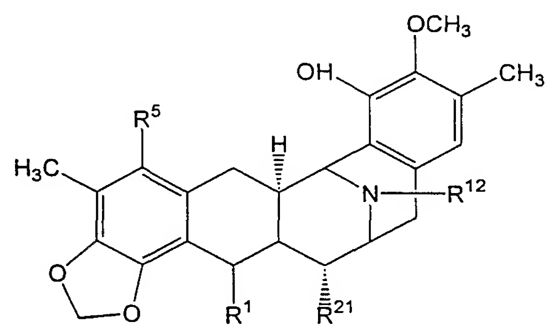


45

Other N-acyl derivatives may readily be made from compound **45** and are an important part of this invention. Suitable acyl groups include those previously mentioned. The corresponding 21-hydroxy compounds are also useful and are among the active compounds which we have found.

From the activity data and other considerations, it can be seen that the active compounds of this invention include a preferred class of compounds of the general formula (XXIII):



where R^1 is as previously defined for formula (XVIIb) and is preferably a derivatised aminomethylene group of moderate bulk;

R^5 is as previously defined for formula (XVIIb) and is preferably a derivatised hydroxy group of low bulk;

R^{12} is as previously defined and is preferably $-CH_3-$; and

R^{21} is a hydroxy or cyano group.

R^1 is suitably a hydrophobic group and which thus lacks free amino, hydroxy or other hydrophilic function. Typically R^1 is a group $-CH_2-NH_2-CO-R^a$, where R^a is as defined but preferably has a linear chain length of less than 20 atoms, more preferably less than 15 or 10 atoms, where a 1,4-phenyl is counted as a chain length of four atoms and similar considerations apply to other cyclic groups (for example, 1,2-cyclohexyl is chain length of two), and the linear chain of less than 10, 15 or 20 atoms can itself be substituted. In particular, the data suggests there is a balance to be achieved between having no such group R^a-CO- and having a large, bulky group.

In one variation, we prefer that R^1 is free from cyclic groups, especially aromatic groups. In a related variation, the present invention does not prepare the compounds which are described in the article Proc. Natl. Acad. Sci. USA, 96, 3496-3501, 1999, incorporated by reference. Our preferred groups for R^1 exclude the corresponding substituents CH_2R_2 shown in Table 1 of that article, specifically the groups A, B, C and D for R_2.

R^5 is preferably an acetyl group.

In particularly preferred compounds, the group R^1 is acylated on an $-NH_2$ group, and for example N-acyl derivatives can be formed from groups $-CH_2NH_2$ and $-CH_2-NH$-aa. The acyl derivatives can be N-acyl or N-thioacyl derivatives thereof. The acyl groups can be of formula $-CO-R^a$, where R^a is as defined and is chosen to meet the indicated criteria. Suitable acyl groups include alanyl, arginyl, aspartyl, asparagyl, cystyl, glutamyl, glutaminyl, glycyl, histidyl, hydroxyprolyl., isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, thyronyl, tryptophyl, tyrosyl, valyl, as well as other amino acid acyl groups, which may be L- or D-. Such amino acid acyl groups are preferred derivatised on the amino group to give hydrophobicity.

In a variation, the group R^1 is a derivatised hydroxymethylene group. Similar considerations apply as with the derivatised aminomethylene group.

The invention extends to compounds where the various substituents around the ring are as defined in the WO 0018233, which we incorporate by reference. Thus, as

appropriate, substituents in the present compounds can be chosen, among other possibilites from H, OH, OR′, SH, SR′, SOR′, SO_2R', NO_2, NH_2, NHR′, $N(R')_2$, NHC(O)R′, CN, halogen, =O, C_1-C_6 alkyl, substituted or unsubstituted aryl, substituted or unsubstituted aralkyl, and substituted or unsubstituted heteroaromatic;

wherein each of the R′ groups is independently selected from the group consisting of H, OH, NO_2, NH_2, SH, CN, halogen, =O, C(=O)H, $C(=O)CH_3$, CO_2H, CO_2CH_3, C_1-C_6 alkyl, phenyl, benzyl and heteroaromatic.

Suitable halogen substituents in the compounds of the present invention include F, Cl, Br and I.

Alkyl groups preferably have from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, and most prefereably 1, 2, 3 or 4 carbon atoms. Methyl, ethyl and propyl including isopropyl are particularly preferred alkyl groups in the compounds of the present invention. As used herein, the term alkyl, unless otherwise modified, refers to both cyclic and noncyclic groups, although cyclic groups will comprise at least three carbon ring members.

Preferred alkenyl and alkynyl groups in the compounds of the present invention have one or more unsaturated linkages and from 2 to about 12 carbon atoms, more preferably 2 to about 8 carbon atoms, still more prefereably 2 to about 6 carbon atoms, even more prefereably 1, 2, 3 or 4 carbon atoms. The terms alkenyl and alkynyl as used herein refere to both cyclic and noncyclic groups, although straight or branched noncyclic groups are generally more preferred.

Preferred alkoxy groups in the compounds of the present invention include groups having one or more oxygem linkages and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms, and most preferably 1, 2, 3 or 4 carbon atoms.

Preferred alkylthio groups in the compounds of the present invention have one or

more thioether linkages and from 1 to about 12 carbon atoms, more prefereably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylthio groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfinyl groups in the compounds of the present invention include those groups having one or more sulfoxide (SO) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfinyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred alkylsulfonyl groups in the compounds of the present invention include those groups having one or more sulfonyl (SO_2) groups and from 1 to about 12 carbon atoms, more preferably from 1 to about 8 carbon atoms, and still more preferably 1 to about 6 carbon atoms. Alkylsulfonyl groups having 1, 2, 3 or 4 carbon atoms are particularly preferred.

Preferred aminoalkyl groups include those groups having one or more primary, secondary and/or tertiary amine groups, and from 1 to about 12 carbon atoms, more preferably 1 to about 8 carbon atoms, still more preferably 1 to about 6 carbon atoms, even more preferably 1, 2, 3 or 4 carbon atoms. Secondary and tertiary amine groups are generally more preferred than primary amine moieties.

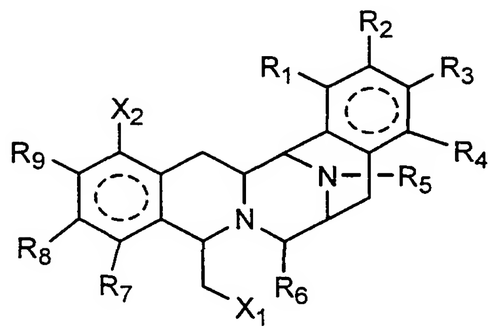
Suitable heteroaromatic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., coumarinyl including 8-coumarinyl, quinolinyl including 8-quinolinyl, pyridyl, pyrazinyl, pyrimidyl, furyl, pyrrolyl, thienyl, thiazolyl, oxazolyl, imidazolyl, indolyl, benzofuranyl and benzothiazol. Suitable heteroalicyclic groups in the compounds of the present invention contain one, two or three heteroatoms selected from N, O or S atoms and include, e.g., tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, morpholino and pyrrolindinyl groups.

Suitable carbocyclic aryl groups in the compounds of the present invention include single and multiple ring compounds, including multiple ring compounds that contain

separate and/or fused aryl groups. Typical carbocyclic aryl groups contain 1 to 3 separate or fused rings and from 6 to about 18 carbon ring atoms. Specifically preferred carbocyclic arykl groups include phenyl including substituted phenyl, such as 2-substituted phenyl, 3-substituted phenyl, 2,3-substituted phenyl, 2,5-substituted phenyl, 2,3,5-substituted and 2,4,5-substituted phenyl, including where one or more of the phenyl substituents is an electron-withdrawing group such as halogen, cyano, nitro, alkanoyl, sulfinyl, sulfonyl and the like; naphthyl including 1-naphthyl and 2-naphthyl; biphenyl; phenanthryl; and anthracyl.

Any references herein to substituted groups in the compounds of the present invention refer to the specified moiety that may be substituted at one or more available positions by one or more suitable groups, e.g., halogen such as fluoro, chloro, bromo and iodide; cyano; hydroxyl; nitro; azido; alkanoyl such as a C1-6 alkanoyl group such as acyl and the like; carboxamido; alkyl groups including those groups having 1 to about °2 carbon atoms or from 1 to about 6 carbon atoms and more preferably 1-3 carbon atoms; alkenyl and alkynyl groups including groups having one or more unsaturated linkages and from 2 to about 12 carbon or from 2 to about 6 carbon atoms; alkoxy groups having those having one or more oxygen linkages and from 1 to about 12 carbon atoms or 1 to about 6 carbon atoms; aryloxy such as phenoxy; alkylthio groups including those moieties having one or more thioether linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbo atoms; alkylsulfinyl groups including those moieties having one or more sulfinyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; alkylsulfinyl groups including those moieties having one or more sulfonyl linkages and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; aminoalkyl groups such as groups having one or more N atoms and from 1 to about 12 carbon atoms or from 1 to about 6 carbon atoms; carbocyclic aryl having 6 or more carbons, particularly phenyl (e.g., R being a substituted or unsubstituted biphenyl moiety); and aralkyl such as benzyl.

Without being exhaustive, in terms of the formula:



preferred compounds of this invention have one or more of the following definitions:

R_1 is -OR, where R is H, acyl, especially acetyl, alkyl-CO- (alkyl being up to about 20 carbon atoms, more preferably from 1 to about 12 carbon atoms, and especially an odd number of carbon atoms such as 3, 5, 7 and 9), cycloalkyl-alkyl-CO- and especially alkyl groupings with a terminal cyclohexyl group and up to six additional carbon atoms in the sidechain, or a protecting group, especially methoxymethyl, and R_1 is more especially OH.

R_2 is methoxy.

R_3 is methyl.

R_4 is hydrogen.

R_5 is methyl or hydrogen, especially methyl.

R_6 is -CN or -OH.

X_1 is –NHR', -NH-aa-R' or –OR' where aa is an optionally protected amino acid acyl group, especially alanine, phenylalanine, cysteine, proline, valine, arginine, tryptophan or other amino acid. Other possibilities for X_1 include –N(R')$_2$, -N(R')-aa-R', and –N-(aa-R')$_2$. In the case of any group –aa-R', the R' is usually on the amino group of the amino acid, and there may be two such substituents. R' is preferably H; alkyl-CO- (alkyl being up to 25 carbon atoms, such as up to 17, 19 or 21 carbon atoms and preferably an odd number of carbon atoms corresponding to a fatty acid carboxylic acid of even number of carbon atoms

or else a low number of carbon atoms such as 1 to 6), especially $CH_3-(CH_2)n-CO-$ where n is for example 1, 2, 4, 12 or 16; alkenyl, especially allyl; haloalkyl-CO-, especially CF_3-CO-; cycloalkyl-alkyl-CO-, preferably alkyl groupings with a terminal cyclohexyl group and up to six additional carbon atoms in the sidechain, especially cyclohexyl-$(CH_2)_n$-CO- where n is for example 1 or 2; haloalkyl-O-CO-, especially trichloroethoxycarbonyl; arylalkyl-CO- or arylalkenyl-CO- especially phenyl-methyl/ethyl/vinyl-CO-, where aryl may be substituted as in trifluoromethylcinnamoyl; optionally substituted heteroaryl-CO-, where the substituents and heterocyclic group are as elsewhere discussed, as in 2-chloronicotinoyl; alkenyl-CO- especially crotonyl; opitionally subsituted aminoalkyl-CO-, particularly amino acid acyl, especially alanine, phenylalanine, cysteine, proline, valine, arginine, tryptophan or other amino acid, or a derivative thereof, as in Boc- phenylalanine, valine, proline, arginine or tryptophan, or as in phenethylalanine, trifluoroethylacetylalanine, trifluorodiacetylalanine and isomers thereof, or diacetyl- or dipropionyl- trifluoroacetyl, or as in or as in Cbz-Val- or a group notionally derived from cysteine and being of general formula $Prot^{SH}$-S-CH_2-C(=NO$Prot^{OH}$)-CO- or $Prot^{SH}$-S-CH=C(-O$Prot^{OH}$)-CO-, where $Prot^{SH}$ and $Prot^{OH}$ are protecting groups for thiol and for hydroxy, especially where $Prot^{SH}$ is Fm and $Prot^{OH}$ is methoxy for the first formulaor MOM for the second formula;or other possibilities such as a protecting group as in an alkoxycarbonyl such as Boc, or PhNR'CS. The various groups may be susbtituted as indicated elsewhere in this specification.

R_7 and R_8 are -O-CH_2-O- or R_7 is =O and R_8 is OMe, especially R_7 and R_8 are -O-CH_2-O-.

R_9 is methyl.

X_2 is –OR", where R" is preferably H; alkyl-CO-, especially acetyl; alkenyl especially allyl; alkenyl-O-CO-, especially allyl-O-CO-; haloalkyl-CO-, especially trifluoromethylcarbonyl or chloromethylcarbonyl or 2-chloroethylcarbonyl or perfluoropropylcarbonyl.

Of special interest are compounds wherein:

R_1 is -OR, where R is H or acetyl, alkyl-CO-, especially n-propyl-CO-, and R_1 is more especially OH.

R_2 is methoxy.

R_3 is methyl.

R_4 is hydrogen.

R_5 is methyl.

R_6 is -CN or -OH.

X_1 is –NHR', where R' is preferably alkenyl, especially allyl, alkyl-CO- (alkyl being 1 to 6 carbon atoms, especially CH_3-(CH_2)n-CO- where n is for example 1 to 6, and more especially 1 to 4); cycloalkyl-alkyl-CO-, especially cyclohexyl-(CH_2)$_n$-CO where n is 1 or 2; arylalkyl-CO- or arylalkenyl-CO- especially phenethylcarbonyl, phenylvinylcarbonyl or benzylcarbonyl, alkenyl-CO- especially CH_3-CH=CH-CO-; amino acid acyl, especially Cbz-Val-; optionally substituted heteroaryl-CO-, especially 2-chloropyridinylcarbonyl;

or X_1 is –NH-aa-R' where aa is alanine, phenylalanine, tryptophan or valine; R` is an amino subsituent and is arylalkyl-CO- especially phenethylcarbonyl or benzylcarbonyl; alkyl-CO- (alkyl being 1 to 6 carbon atoms, especially CH_3-(CH_2)n-CO- where n is for example 1 to 6 and more especially 1, 2 or 4; alkenyl-CO- especially CH_3-CH=CH-CO-; or protecting group especially alkyloxy-CO as in Boc;

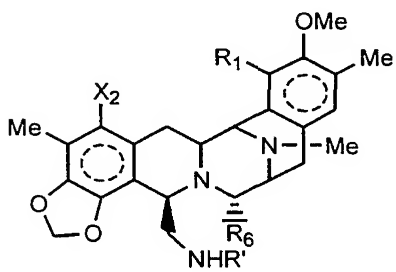
or X_1 is –OR' where R' is preferably alkyl-CO- (alkyl being 1 to 6 carbon atoms, especially CH_3-(CH_2)n-CO- where n is for example 1 to 6, and more especially 2; arylalkyl-CO- or arylalkenyl-CO- especially phenethylcarbonyl, phenylvinylcarbonyl or trifluoromethylcinnamoyl.

R_7 and R_8 are -O-CH_2-O-.

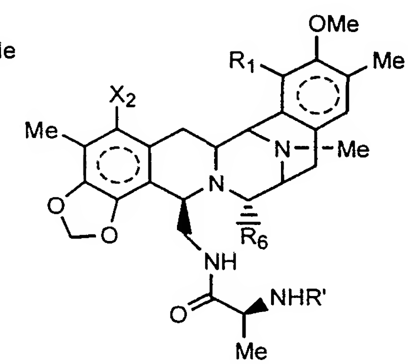
R_9 is methyl.

X_2 is –OR", where R" is H; acetyl, allyloxycarbonyl, chloromethylcarbonyl or perfluoropropylcarbonyl; and R" is more especially H; acetyl or allyloxycarbonyl.

Especially preferred embodiments of the present invention are the novel ecteinascidin-like compounds with the following general structures I, II and III that have been prepared from compounds 17, 25, 43 and 45 derived from cyanosafracin B. Compound 25 corresponds to the synthetic intermediate 3 described in US patent No 6,124,292.



(I)



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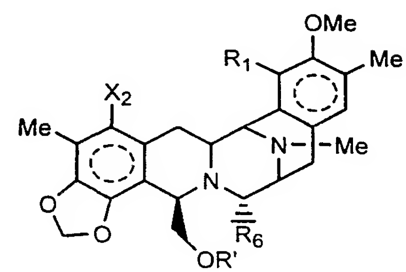


(III)

Wherein R', X_2, R_1 and R_6 are each independently selected from the groups defined below:

R'	X_2	R_1	R_6
H	OH	OH	CN
$CH_2CH{=}CH_2$	OAc	OAc	OH
$COCH_2CH_3$	$OCH_2CH{=}CH_2$	OMOM	
$COCH_2CH_2CH_3$	$OCOOCH_2CH{=}CH_2$	$OCOCH_2C_6H_{11}$	
$CO(CH_2)_4CH_3$	$OCOCF_3$	$OCOCH_2CH_2C_6H_{11}$	
$CO(CH_2)_{12}CH_3$	$OCOCH_2Cl$	$OCOCH_2CH_2CH_3$	
$CO(CH_2)_{16}CH_3$	$OCOCH_2CH_2Cl$	$OCO(CH_2)_4CH_3$	

$COCH_2C_6H_{11}$

$COCH_2CH_2C_6H_{11}$

$COOCH_2CCl_3$

$COCH_2Ph$

$COCH_2CH_2Ph$

$COCH{=}CHCH_3$

$COCH{=}CHPh$

$COCH{=}CHArCF_3$

$COCH(CH_3)NHCOCH_2CH_2Ph$

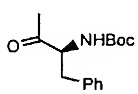
$CO\text{-}(S)\text{-}CH(CH_3)NHCOCF_3$

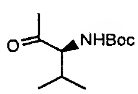
$CO\text{-}(R)\text{-}CH(CH_3)NHCOCF_3$

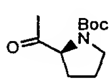
$CO\text{-}(S)\text{-}CH(NHCbz)CH(CH_3)_2$

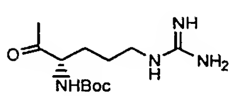
Boc

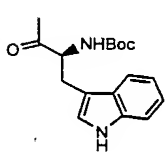
CSNHPh

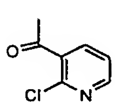












$OCOCF_2CF_2CF_3$

$OCO(CH_2)_8CH_3$

$OCO(CH_2)_{16}CH_3$

In the formulae (XVIIa) or (XVIIb), R^1 is typically aminomethylene, amidomethylene or R^1 with R^4 forms a group (IV) or (V). Suitable amidomethylene groups include those of formula $-CH_2\text{-}NH\text{-}CO\text{-}CHCH_3\text{-}NH_2$ derived from alanine, and similar groups derived from other amino acids, notably , both D and L, glycine, valine, leucine, isoleucine, phenylalanine,

tyrosine, tryptophan, methionine, cysteine, aspartate, asparagine, glutamatic acid, glutamine, lysine, arginine, proline, serine, threonine, histidine and hydroxyproline. A general formula for the group R^1 is then -CH_2-NH -aa, where aa indicates an acyl amino acid group.

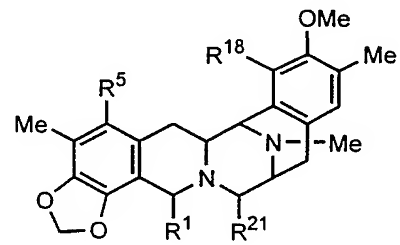
The group R^1 can be acylated on an -NH_2 group, and for example N-acyl derivatives can be formed from groups -CH_2NH_2 and -CH_2-NH-aa. The acyl derivatives can be N-acyl or N-thioacyl derivatives thereof, as well as cyclic amides. The acyl groups can illustratively be alkanoyl, haloalkanoyl, arylalkanoyl, alkenoyl, heterocyclylacyl, aroyl, arylaroyl, haloaroyl, nitroaroyl, or other acyl groups. The acyl groups can be of formula -CO-R^a, where R^a can be various groups such as alkyl, alkoxy, alkylene, arylalkyl, arylalkylene, amino acid acyl, or heterocyclyl, each optionally substituted with halo, cyano, nitro, carboxyalkyl, alkoxy, aryl, aryloxy, heterocyclyl, heterocyclyloxy, alkyl, amino or substituted amino. Other acylating agents include isothiocyanates, such as aryl isothiocyanates, notably phenyl isocyanate. The alkyl, alkoxy or alkylene groups of R^a suitably have 1 to 6 or 12 carbon atoms, and can be linear, branched or cyclic. Aryl groups are typically phenyl, biphenyl or naphthyl. Heterocyclyl groups can be aromatic or partially or completely unsaturated and suitably have 4 to 8 ring atoms, more preferably 5 or 6 ring atoms, with one or more heteroatoms selected from nitrogen, sulphur and oxygen.

Without being exhaustive, typical R^a groups include alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, arylalkylene, haloalkylarylakylene, acyl, haloacyl, arlyalkyl, alkenyl and amino acid. For example, R^a-CO- can be acetyl, trifluoroacetyl, 2,2,2-trichloroethoxycarbonyl, isovalerylcarbonyl, trans-3-(trifluoromethyl)cinnamoylcarbonyl, heptafluorobutyrylcarbonyl, decanoylcarbonyl, trans-cinnamoylcarbonyl, butyrylcarbonyl, 3-chloropropyonylcarbonyl, cinnamoylcarbonyl, 4-methylcinnamoylcarbonyl, hydrocinnamoylcarbonyl, or trans-hexenoylcarbonyl, or alanyl, arginyl, aspartyl, asparagyl, cystyl, glutamyl, glutaminyl, glycyl, histidyl, hydroxyprolyl., isoleucyl, leucyl, lysyl, methionyl, phenylalanyl, prolyl, seryl, threonyl, thyronyl, tryptophyl, tyrosyl, valyl, as well as other less common amino acid acyl groups, as well as phthalimido and other cyclic amides. Other examples may be found among the listed protecting groups.

Compounds wherein -CO-R^a is derived from an amino acid and include an amino

group can themselves form acyl derivatives. Suitable N-acyl commands include dipeptides which in turn can form N-acyl derivatives.

In an important aspect of this invetnion, there are provided preferred compounds of the formula:



wherein:

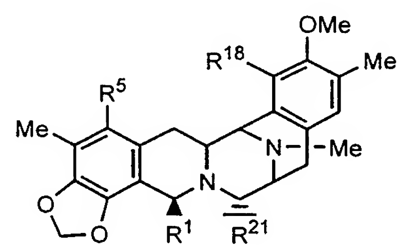
R^1 is $-CH_2-N(R^a)_2$ or $-CH_2-OR^a$, where R^a is H; alkyl-CO-; haloalkyl-CO-; cycloalkylalkyl-CO-; haloalkyl-O-CO-; arylalkyl-CO-; arylalkenyl-CO-; heteroaryl-CO-; alkenyl-CO-; alkenyl; amino acid acyl; or a protecting group;

R^5 is –OR", where R" is H; alkyl-CO-; cycloalkyl-CO-; haloalkyl-CO- or a protecting group;

R^{18} is -OR, where R is H, alkyl-CO-; cycloalkylalkyl-CO-; or a protecting group;

R^{21} is –CN or –OH.

Typically such a compound is of the formula:



wherein R^1, R^5, R^{18}, and R^{21} are as defined.

In such preferred compounds of this invention, R^1 can be $-CH_2-NHR^a$.

R^a can be $-aa-R^b$ where aa is amino acid acyl and R^b is as defined for R^a. The amino acid acyl is optionally further substituted with one or more R^a groups.

In further preferred comopunds, R^1 is $-CH_2$-NH-aa-R^b where aa is an amino acid and R^b is hydrogen; protecting group; arylalkenyl-CO-; haloalkyl-CO-; alkyl-CO-; arylalkyl-CO-; or amino acid acyl. Such comopunds include those wherein R^1 is $-CH_2$-NH-aa-R^b where aa is alanine and R^b is hydrogen, Boc, PhNHCS-, CF_3CO-, PhNAcCS-, trifluorocinnamoyl, cinnamoyl, C_3F_7CO-, butyryl, 3-chloroproprionoyl, hydrocinnamoyl, hexanoyl, phenylacetyl, Cbz-val or acetyl; $-CH_2$-aa-R^b where aa is valine and R^b is Cbz or Boc; $-CH_2$-aa-R^b where aa is phenylalanine and R^b is Boc; $-CH_2$-aa-R^b where aa is proline and R^b is Boc; $-CH_2$-aa-R^b where aa is arginine and R^b is Boc; or $-CH_2$-aa-R^b where aa is tryptophan and R^b is Boc.

R^1 can be $-CH_2$-NR^a-aa-R^b where aa is an amino acid, R^a is alkyl-CO- and R^b is haloalkyl-CO-. Such compounds include those wherein R^1 is $-CH_2$-NR^a-aa-R^b where aa is acetylalanine, R^a is acetyl or butyryl, and R^b is CF_3-CO-.

R^1 can be $-CH_2$-NHR^a where R^a is hydrogen, protecting group, alkyl-CO-; alkenyl-CO-; arylalkenyl-CO-; arylalkyl-CO-; heteroaryl-CO-; cycloalkylalkyl-CO-; or alkenyl. Such compounds include those wherein R^1 is $-CH_2$-NHR^a where R^a is hydrogen, Troc, acetyl; isovaleroyl, decanoyl, cinnamoyl, hydrocinnamoyl, phenylacetyl, propionyl, myristoyl, stearoyl, hexanoyl, crotonyl, chloronicotinoyl, cyclohexylacetyl, cyclohexylpropionyl or allyl.

R^1 can be $-CH_2$-OR^a where R^a is hydrogen; a protected cysteine; a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C($NHProt^{NH}$)-CO-, where $Prot^{SH}$ and $Prot^{NH}$ are protecting groups for thiol and for amino; a protecting group; alkyl-CO-; arylalkyl-CO-; arylalkenyl-CO-;

a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C(=$NOProt^{OH}$)-CO- where $Prot^{SH}$ and $Prot^{OH}$ are protecting groups for thiol and for hydroxy; or a cysteine derivative of formula $Prot^{SH}$-S-CH=C(-$OProt^{OH}$)-CO-, where $Prot^{SH}$ and $Prot^{OH}$ are protecting groups for thiol and for hydroxy. Such compounds include those wherein R^1 is $-CH_2$-OR^a where R^a is hydrogen; S-Fm-O-TBDMS-cysteine;a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C($NHProt^{NH}$)-CO-, where $Prot^{SH}$ is Fm and $Prot^{OH}$ is Troc; TBDPS; butyryl; trfiluormethylcinnamoyl; cinnamoyl; hydrocinnamoyl; a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-

C(=NOProt^{OH})-CO- where Prot^{SH} is Fm and Prot^{OH} is methoxy; or a cysteine derivative of formula Prot^{SH}-S-CH=C(-OProt^{OH})-CO-, where Prot^{SH} is Fm and Prot^{OH} is MOM.

In these preferred compounds, R^5 is suitably –OR", where R" is H; alkyl-CO where the alkyl has an odd number of carbon atoms, ω-cyclohexylalkyl-CO-; or a protecting group.

In these preferred compounds, R^{18} is suitably -OR, where R is H, alkyl-CO-; or a protecting group;

In one variation which relates to intermediate products, the ring A is modified to incorporate the substructure shown as formula (XX) or (XXI), discussed later.

In another variation relating to intermediates, the group R^1 can be -CH_2O-CO-CFu-CH_2-S-Prot^3, derived from a compound of formula (XIX), where Prot^3 and Fu have the indicated meanings. In such a case, R^7 and R^8 from the oxymethyleneoxy group. The group R^{18} is usually protected. Usually R^{21} is cyano.

Preferably R^{14a} and R^{14b} are hydrogen. Preferably R^{15} is hydrogen. The O-acyl derivatives are suitably aliphatic O-acyl derivatives, especially acyl derivatives of 1 to 4 carbon atoms, and typically an O-acetyl group, notably at the 5-position.

Suitable protecting groups for phenols and hydroxy groups include ethers and esters, such as alkyl, alkoxyalkyl, aryloxyalkyl, alkoxyalkoxyalkyl, alkylsilylalkoxyalkyl, alkylthioalkyl, arylthioalkyl, azidoalkyl, cyanoalkyl, chloroalkyl, heterocyclic, arylacyl, haloarylacyl, cycloalkylalkyl, alkenyl, cycloalkyl, alyklarylalkyl, alkoxyarylalkyl, nitroarylalkyl, haloarylalkyl, alkylaminocarbonylarylalkyl, alkylsulfinylarylalky, alkylsilyl and other ethers, and arylacyl, aryl alkyl carbonate, aliphatic carbonate, alkylsulfinylarlyalkyl carbonate, alkyl carbonate, aryl haloalkyl carbonate, aryl alkenyl carbonate, aryl carbamate, alkyl phosphinyl, alkylphosphinothioyl, aryl phosphinothioyl, aryl alkyl sulphonate and other esters. Such groups may optionally be substituted with the previously mentioned groups in R^1.

Suitable protecting groups for amines include carbamates, amides, and other protecting groups, such as alkyl, arylalkyl, sulpho- or halo- arylalkyl, haloalkyl, alkylsilylalkyl, arylalkyl, cycloalkylalkyl, alkylarylalkyl, heterocyclylalkyl, nitroarylalkyl, acylaminoalkyl, nitroaryldithioarylalkyl, dicycloalkylcarboxamidoalkyl, cycloalkyl, alkenyl, arylalkenyl, nitroarylalkenyl, heterocyclylalkenyl, heterocyclyl, hydroxyheterocyclyl, alkyldithio, alkoxy- or halo- or alkylsulphinyl arylalkyl, hetercyclylacyl, and other carbamates, and alkanoyl, haloalkanoyl, arylalkanoyl, alkenoyl, heterocyclylacyl, aroyl, arylaroyl, haloaroyl, nitroaroyl, and other amides, as well as alkyl, alkenyl, alkylsilylalkoxyalkyl, alkoxyalkyl, cyanoalkyl, heterocyclyl, alkoxyarylalkyl, cycloalkyl, nitroaryl, arylalkyl, alkoxy- or hydroxy- arylalkyl, and many other groups. Such groups may optionally be substituted with the previously mentioned groups in R^1.

Examples of such protecting groups are given in the following tables.

protection for -OH group

ethers	abbreviation
methyl	
methoxymethyl	MOM
benzyloxymethyl	BOM
methoxyethoxymethyl	MEM
2-(trimethylsilyl)ethoxymethyl	SEM
methylthiomethyl	MTM
phenylthiomethyl	PTM
azidomethyl	
cyanomethyl	
2,2-dichloro-1,1-difluoroethyl	
2-chloroethyl	
2-bromoethyl	
tetrahydropyranyl	THP
1-ethoxyethyl	EE

phenacyl	
4-bromophenacyl	
cyclopropylmethyl	
allyl	
propargyl	
isopropyl	
cyclohexyl	
t-butyl	
benzyl	
2,6-dimethylbenzyl	
4-methoxybenzyl	MPM or PMB
o-nitrobenzyl	
2,6-dichlorobenzyl	
3,4-dichlorobenzyl	
4-(dimethylamino)carbonylbenzyl	
4-methylsuflinylbenzyl	Msib
9-anthrylmethyl	
4-picolyl	
heptafluoro-*p*-tolyl	
tetrafluoro-4-pyridyl	
trimethylsilyl	TMS
t-butyldimethylsilyl	TBDMS
t-butyldiphenylsilyl	TBDPS
triisopropylsilyl	TIPS

esters

aryl formate	
aryl acetate	
aryl levulinate	
aryl pivaloate	ArOPv

aryl benzoate	
aryl 9-fluorocarboxylate	
aryl methyl carbonate	
1-adamantyl carbonate	
t-butyl carbonate	BOC-OAr
4-methylsulfinylbenzyl carbonate	Msz-Oar
2,4-dimethylpent-3-yl carbonate	Doc-Oar
aryl 2,2,2-trichloroethyl carbonate	
aryl vinyl carbonate	
aryl benzyl carbonate	
aryl carbamate	
dimethylphosphinyl	Dmp-OAr
dimethylphosphinothioyl	Mpt-OAr
diphenylphosphinothioyl	Dpt-Oar
aryl methanesulfonate	
aryl toluenesulfonate	
aryl 2-formylbenzenesulfonate	

protection for the -NH_2 group

carbamates	abbreviation
methyl	
ethyl	
9-fluorenylmethyl	Fmoc
9-(2-sulfo)fluroenylmethyl	
9-(2,7-dibromo)fluorenylmethyl	
17-tetrabenzo[*a,c,g,i*]fluorenylmethyl	Tbfmoc

2-chloro-3-indenylmethyl	Climoc
benz[*f*]inden-3-ylmethyl	Bimoc
2,7-di-*t*-butyl[9-(10,10-dioxo-10,10,10,10-tetrahydrothioxanthyl)]methyl	DBD-Tmoc
2,2,2-trichloroethyl	Troc
2-trimethylsilylethyl	Teoc
2-phenylethyl	hZ
1-(1-adamantyl)-1-methylethyl	Adpoc
2-chlooethyl	
1,1-dimethyl-2-chloroethyl	
1,1-dimethyl-2-bromoethyl	
1,1-dimethyl-2,2-dibromoethyl	DB-*t*-BOC
1,1-dimethyl-2,2,2-trichloroethyl	TCBOC
1-methyl-1-(4-biphenyl)ethyl	Bpoc
1-(3,5-di-*t*-butylphenyl)-1-1-methylethyl	*t*-Burmeoc
2-(2'-and 4'-pyridyl)ethyl	Pyoc
2,2-bis(4'-nitrophenyl)ethyl	Bnpeoc
n-(2-pivaloylamino)-1,1-dimethylethyl	
2-[(2-nitrophenyl)dithio]-1-phenylethyl	NpSSPeoc
2-(*n,n*-dicyclohexylcarboxamido)ethyl	
t-butyl	BOC
1-adamantyl	1-Adoc
2-adamantyl	2-Adoc
vinyl	Voc
allyl	Aloc or Alloc
1-isopropylallyl	Ipaoc
cinnamyl	Coc
4-nitrocinnamyl	Noc
3-(3'-pyridyl)prop-2-enyl	Paloc
8-quinolyl	
n-hydroxypiperidinyl	
alkyldithio	

benzyl	Cbz or Z
p-methoxybenzyl	Moz
p-nitrobenzyl	PNZ
p-bromobenzyl	
p-chlorobenzyl	
2,4-dichlorobenzyl	
4-methylsulfinylbenzyl	Msz
9-anthrylmethyl	
diphenylmethyl	
phenothiazinyl-(10)-carbonyl	
n'-*p*-toluenesulfonylaminocarbonyl	
n'-phenylaminothiocarbonyl	

amides

formamide	
acetamide	
chloroacetamide	
trifluoroacetamide	TFA
phenylacetamide	
3-phenylpropanamide	
pent-4-enamide	
picolinamide	
3-pyridylcarboxamide	
benzamide	
p-phenylbenzamide	
n-phthalimide	
n-tetrachlorophthalimide	TCP
4-nitro-*n*-phthalimide	
n-dithiasuccinimide	Dts
n-2,3-diphenylmaleimide	
n-2,5-dimethylpyrrole	

n-2,5-bis(triisopropylsiloxyl)pyrrole	BIPSOP
n-1,1,4,4-tetramethyldisiliazacyclopentante adduct	STABASE
1,1,3,3-tetramethyl-1,3-disilaisoindoline	BSB

special -NH protective groups

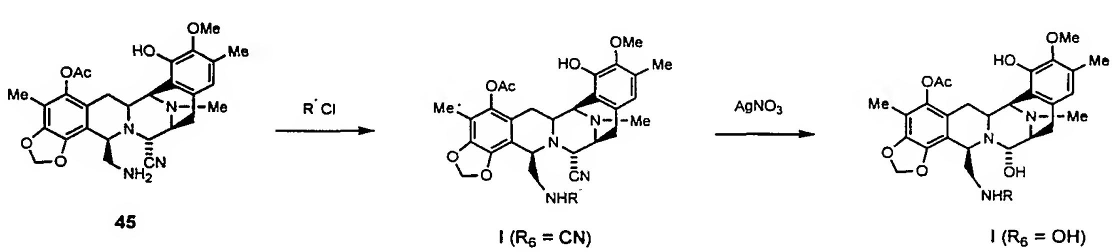
n-methylamine	
n-*t*-butylamine	
n-allylamine	
n-[2-trimethylsilyl)ethoxy]methylamine	SEM
n-3-acetoxypropylamine	
n-cyanomethylamine	
n-(1-isopropyl-4-nitro-2-oxo-3-pyrrolin-3-yl)amine	
n-2,4-dimethoxybenzylamine	Dmb
2-azanorbornenes	
n-2,4-dinitrophenylamine	
n-benzylamine	Bn
n-4-methoxybenzylamine	MPM
n-2,4-dimethoxybenzylamine	DMPM
n-2-hydroxybenzylamine	Hbn
n-(diphenylmethyl)amino	DPM
n-bis(4-methoxyphenyl)methylamine	
n-5-dibenzosuberylamine	DBS
n-triphenylmethylamine	Tr
n-[(4-methoxyphenyl)diphenylmethyl]amino	MMTr
n-9-phenylflurenylamine	Pf
n-ferrocenylmethylamine	Fcm
n-2-picolylamine *n'*-oxide	
n-1,1-dimethylthiomethyleneamine	
n-benzylideneamine	
n-*p*-methoxybenzylideneamine	
n-diphenylmethyleneamine	

n-(5,5-dimethyl-3-oxo-1-cyclohexenyl)amine	
n-nitroamine	
n-nitrosoamine	
diphenylphosphinamide	Dpp
dimethylthiophosphinamide	Mpt
diphenylthiophosphinamide	Ppt
dibenzyl phosphoramidate	
2-nitrobenzenesulfenamide	Nps
n-1-(2,2,2-trifluoro-1,1-diphenyl)ethylsufenamide	TDE
3-nitro-2-pyridinesulfenamide	Npys
p-toluenesulfonamide	Ts
benzenesulfonamide	

Examples of preferred methods of this invention will firstly be considered with reference to starting compunds 45, 43 and 25. It will be appreicated that the particular substituents, notably at positions C-5 and C-18, can be varied in the light of the present disclosure.

The preferred methods of producing the compounds of formula I, II and III are described below in the following reaction schemes with examples of typical substituent groups.

Scheme 1



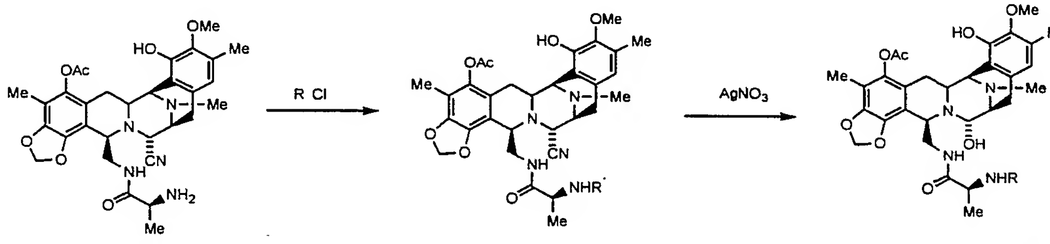
As illustrated in Scheme 1 the first step for producing the preferred compounds (I) (where R_1 = OH, X_2 = OAc and R_6 = CN or OH) of the present invention from compound

45 is the high yielding conversion of the amino group to the amide group.

After acylation of the amino group the second step is the transformation of the CN group into an OH group by reaction with silver nitrate in AcCN/H_2O.

The preparation of other compounds of the general formula I of the present invention starting from compound 17 is described below (Scheme 4).

Scheme 2

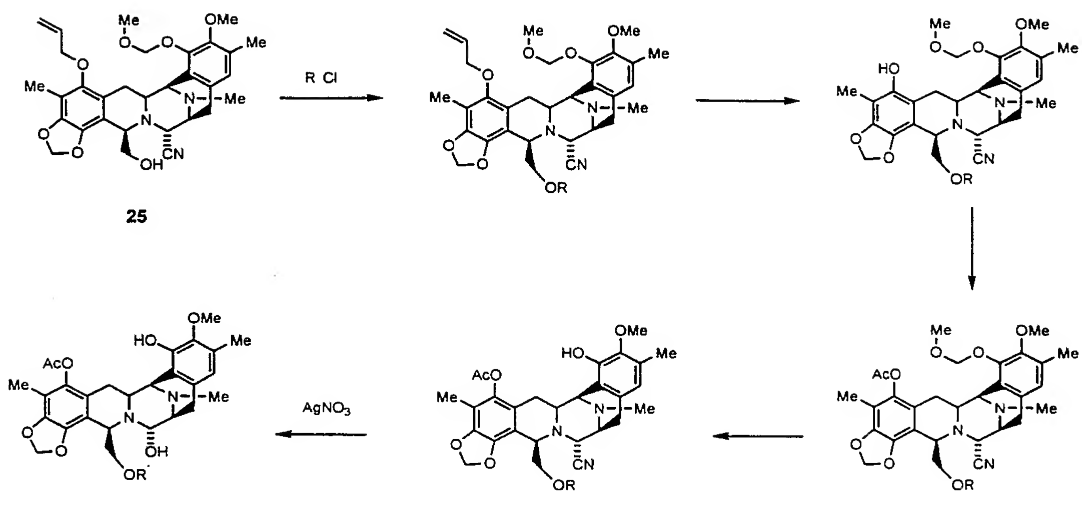


43 II (R_6 = CN) II (R_6 = OH)

As illustrated in Scheme 2 another group of interesting derivatives with formula II (where R_1 = OH, X_2 = OAc and R_6 = CN or OH) can be obtained from compound 43 using the following sequence. Acylation of the amino group to provide the corresponding amide and transformation of the CN group into an OH group by reaction with silver nitrate in AcCN/H2O.

The preparation of other compounds of the general formula II of the present invention starting from compound 17 is described below (Scheme 4).

<u>Scheme 3</u>

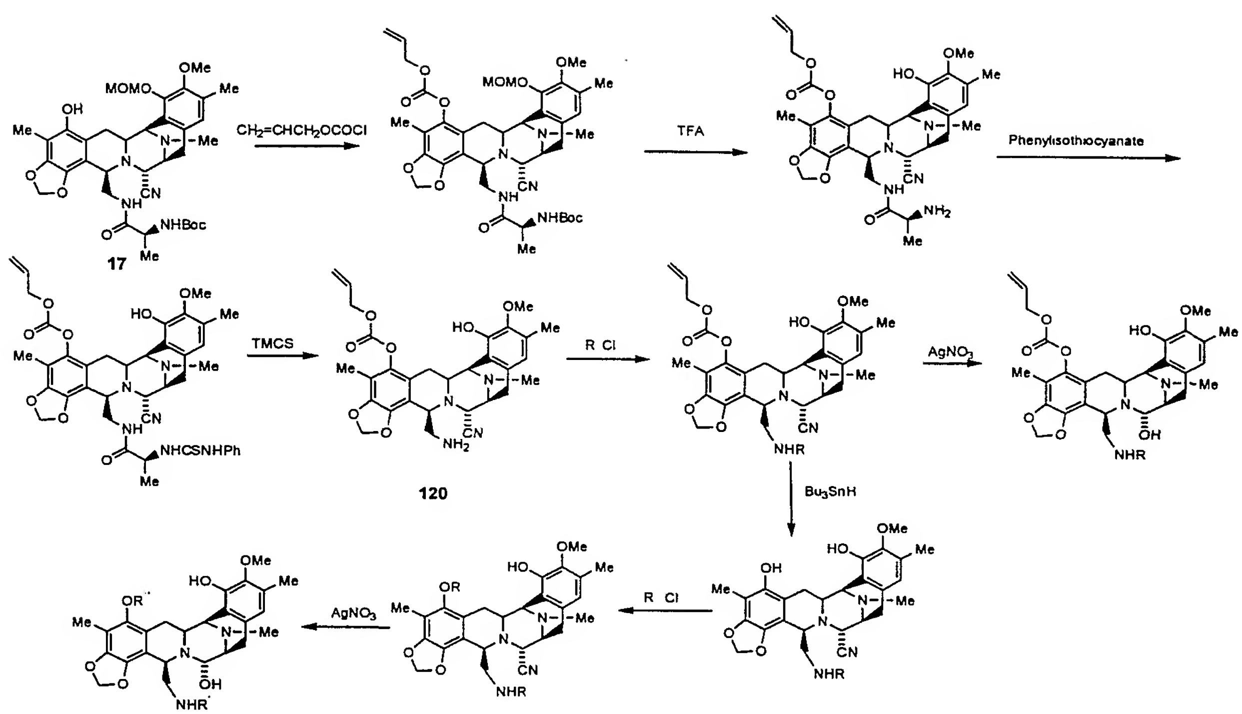


III

The preferred procedure for producing compounds of formula III is the transformation of compound 25 into the corresponding ester derivatives by acylation of the OH group, deprotection of the phenol group followed by acetylation and deprotection of the MOM group to provide the corresponding ester followed by transformation of the CN group to the OH group by reaction with silver nitrate in AcCN/H_2O to give the compound of formula III (where R_1 = OH, X_2 = OAc and R_6 = CN or OH) .

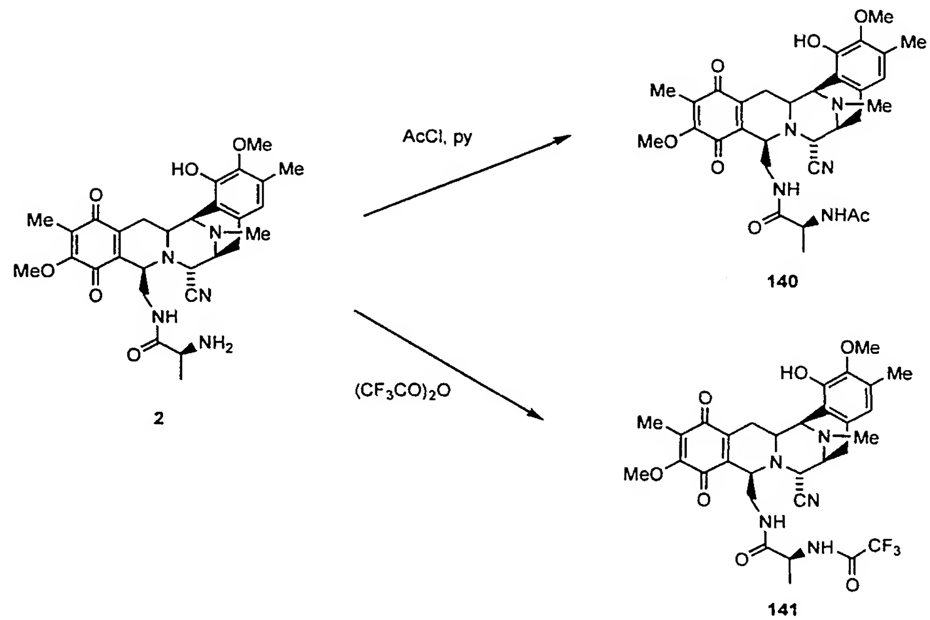
Other compounds of the general formulae I and II of the present invention can be prepared from compound 17 via the amine intermediate 120 as described in Scheme 4.

Scheme 4



The following additional compounds of the present invention (including for example 140 and 141) have been prepared starting from cyanosafracin B (2) as described in detail in the examples (Scheme 5).

Scheme 5



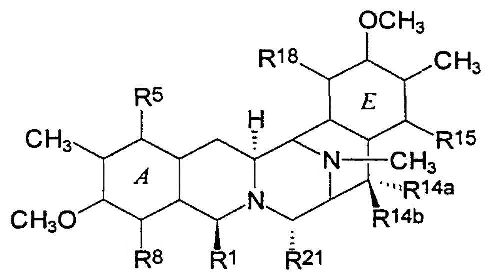
As the skilled artisan will readily appreciate, the reaction schemes described herein may be modified and/or combined in various ways, and the compounds generated therefore are to be considered as being part of this invention. In particular the starting material and/or reagents and reactions can be varied to suit other combinations of the substituent groups in the formulae I, II and III.

In a related aspect, the present invention is directed at the use of a known compound, safracin B, also referred to as quinonamine, in hemisynthetic synthesis.

More generally, the invention relates to a hemisynthetic process for the formation of intermediates, derivatives and related structures of ecteinascidin or other tetrahydroisoquinolinephenol compounds starting from natural bis(tetrahydroisoquinoline) alkaloids. Suitable starting materials for the hemi-synthetic process include the classes of

saframycin and safracin antibiotics available from different culture broths, and also the classes of reineramicin and xestomycin compounds available from marine sponges.

A general formula (XV) for the starting compounds is as follows:



where:

R^1 is an amidomethylene group such as $-CH_2-NH-CO-CR^{25a}R^{25b}R^{25c}$ where R^{25a} and R^{25b} form a keto group or one is -OH, $-NH_2$ or $-OCOCH_3$ and the other is $-CH_2COCH_3$, -H, -OH or $-OCOCH_3$, provided that when R^{25a} is -OH or $-NH_2$ then R^{25b} is not -OH, and R^{25c} is -H, $-CH_3$ or $-CH_2CH_3$, or R^1 is an acyloxymethylene group such as $-CH_2-O-CO-R$, where R is $-C(CH_3)=CH-CH_3$ or $-CH_3$;

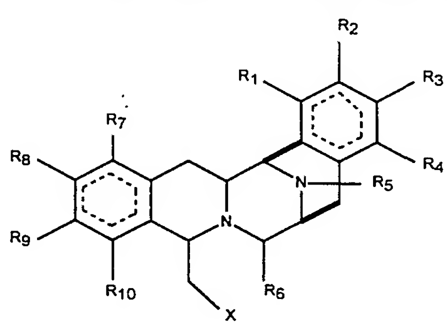
R^5 and R^8 are independently chosen from -H, -OH or $-OCOCH_2OH$, or R^5 and R^8 are both keto and the ring *A* is a p-benzoquinone ring;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group;

R^{15} and R^{18} are independently chosen from -H or -OH, or R^5 and R^8 are both keto and the ring *A* is a p-benzoquinone ring; and

R^{21} is -OH or -CN.

A more general formula for these class of compounds is provided below:



wherein the substituent groups defined by R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10} are each

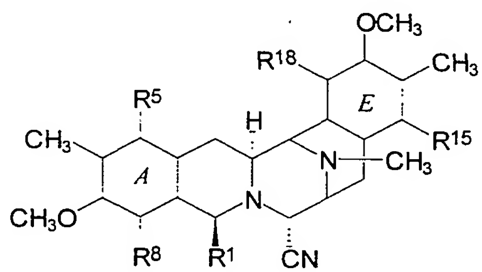
independently selected from the group consisting of H, OH, OCH_3, CN, =O, CH_3;

wherein X are the different amide or ester functionalities contained in the mentioned natural products;

wherein each dotted circle represents one, two or three optional double bonds.

Thus, according to the present invention, we now provide hemisynthetic routes for the production of intermediates including Intermediate 11 and thus for the production of the ecteinascidin compounds as well as phthalascidin and additional compounds. The hemisynthetic routes of the invention each comprise a number of transformation steps to arrive at the desired product. Each step in itself is a process in accordance with this invention. The invention is not limited to the routes that are exemplified, and alternative routes may be provided by, for example, changing the order of the transformation steps, as appropriate.

In particular, this invention involves the provision of a 21-cyano starting material of general formula (XVI):



where R^1, R^5, R^8, R^{14a}, R^{14b}, R^{15} and R^{18} are as defined.

Other compounds of formula (XVI) with different substituents at the 21-position may also represent possible starting materials. In general, any derivative capable of production by nucleophilic displacement of the 21-hydroxy group of compounds of formula (XV) wherein R^{21} is a hydroxy group cis a candidate. Examples of suitable 21-substituents include but are not limited to:

a mercapto group;

an alkylthio group (the alkyl group having from 1 to 6 carbon atoms);

an arylthio group (the aryl group having from 6 to 10 carbon atoms and being unsubstituted

or substituted by from 1 to 5 substituents selected from, for example, alkyl group having from 1 to 6 carbon atoms, alkoxy groups having from 1 to 6 carbon atoms, halogen atoms, mercapto groups and nitro groups);

an amino group;

a mono-or dialkylamino (the or each alkyl group having from 1 to 6 carbon atoms);

a mono-or diarylamino group (the or each aryl group being as defined above in relation to arylthio groups);

an α-carbonylalkyl group of formula $-C(R^a)(R^b)-C(=O)R^c$, where

R^a and R^b are selected from hydrogen atoms, alkyl groups having from 1 to 20 carbon atoms, aryl groups (as defined above in relation to arylthio groups) and aralkyl groups (in which an alkyl group having from 1 to 4 carbon atoms is substituted by an aryl group a defined above in relation to arylthio groups), with the proviso that one of R^a and R^b is a hydrogen atom;

R^c is selected from a hydrogen atom, an alkyl group having from 1 to 20 carbon atoms, aryl groups (as defined above in relation to arylthio groups), an aralkyl group (in which an alkyl group having from 1 to 4 carbon atoms is substituted by an aryl group a defined above in relation to arylthio groups), an alkoxy group having from 1 to 6 carbon atoms, an amino group or a mono- or dialkylamino group as defined above.

Thus, in a more general aspect, the present invention relates to processes where the first step is to form a 21-deriviative using a nucleophilic reagent. We refer to such compounds as 21-Nuc compounds.

The presence of the 21-cyano group is required for some of the end-products, notably ecteinascidin 770 and phthalascidin, while for other end-products it acts as a protecting group which can readily be converted to another substituent, such as the 21-hydroxy group of ecteinascidin 743 or of 21-hydroxyphthalascidin. The adoption of the 21-cyano compound as the starting material effectively stabilises the molecule during the ensuing synthetic steps, until it is optionally removed. Other 21-Nuc compounds can offer this and other advantages.

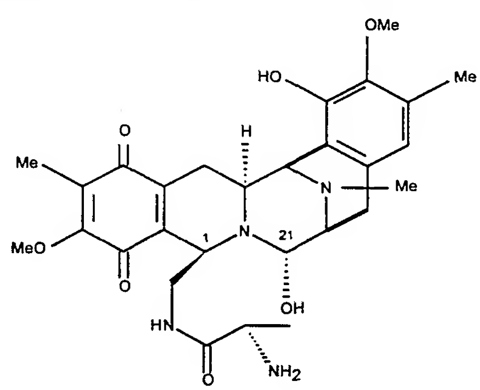
In one important aspect, the present invention consists in the use of a 21-cyano compound of the general formula (XVI) in the preparation of a bis- or tris-

(tetrahydroisoquinolinephenol) compounds. Products which may be prepared include intermediates such as Intermediate 11, and the ecteinascidins and phthalascidin, as well as new and known compounds of related structure.

Preferred starting materials include those compounds of formula (XV) or (XVI) where R^{14a} and R^{14b} are both hydrogen. Preferred starting materials also include compounds of formula (XV) or (XVI) where R^{15} is hydrogen. Furthermore, the preferred starting materials include compounds of formula (XV) or (XVI) where ring *E* is a phenolic ring. Preferred starting materials further include compounds of formula (XV) or (XVI) where at least one, better at least two or three of R^5, R^8, R^{15} and R^{18} is not hydrogen.

Examples of suitable starting materials for this invention include saframycin A, saframycin B, saframycin C, saframycin G, saframycin H, saframycin S, saframycin Y_3, saframycin Yd_1, saframycin Ad_1, saframycin Yd_2, saframycin AH_2, saframycin AH_2Ac, saframycin AH_1, saframycin AH_1Ac, saframycin AR_3, renieramycin A, renieramycin B, renieramycin C, renieramycin D, renieramycin E, renieramycin F, xestomycin, saframycin D, saframycin F, saframycin Mx-1, saframycin Mx-2, safracin A, safracin B and saframycin R. Preferred starting materials have a cyano group in position 21, for the group R^{21}.

In a particularly preferred aspect, the invention involves a hemisynthetic process wherein the transformation steps are applied to safracin B:



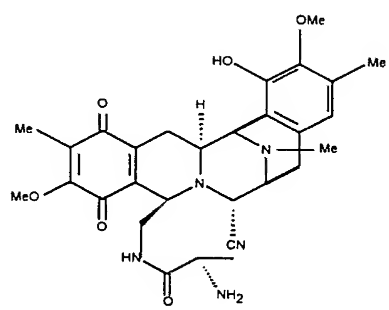
SAFRACIN B

Safracin B presents a ring system closely related to the ecteinascidins. This

compound has the same pentacycle structure and the same substitution pattern in the right-hand aromatic ring, ring *E*. Also, safracin B presents very close similarities to some of the synthetic intermediates in the total synthesis of ET-743, particularly to the intermediate 11. Such intermediate can be transformed into Et-743 using a well established method. Synthetic conversion of safracin B into intermediate 11 will therefore provide an hemi-synthetic method to obtain ET-743.

Thus, we provide Intermediate 11 made from this compound safracin B, and compounds derived from Intermediate 11, particularly ecteinascidin compounds. We further provide phthalascidin made from safracin B. The invention also relates to use of safracin B in the production of Intermediate 11, phthalascidin, ecteinascidin compounds and the other intermediates of the invention. The invention also relates to compounds described herein derived from the other suggested starting materials, and use of those compounds in the production of such compounds.

The more preferred starting materials of this invention have a 21-cyano group. The currently most preferred compound of the present invention is the compound of Formula **2**. This compound is obtained directly from safracin B and is considered a key intermediate in the hemisynthetic process.



compound 2

In a related aspect, we provide cyanosafracin B by fermentation of a safracin B-producing strain of *Pseudomonas fluorescens*, and working up the cultured broth using cyanide ion. The preferred strain of *Pseudomonas fluorescens* is strain A2-2, FERM BP-14, which is employed in the procedure of EP 055,299. A suitable source of cyanide ion is potassium cyanide. In a typical work-up, the broth is filtered and excess cyanide ion is

added. After an appropriate interval of agitation, such as 1 hour, the pH is rendered alkaline, say pH 9.5, and an organic extraction gives a crude extract which can be further purified to give the cyanosafracin B.

Safracin B includes an alanyl sidechain. In one aspect of the invention, we have found that protection of the free amino group with a Boc group can give strong advantages.

In general, the conversion of the 21-cyano starting compound to an ecteinascidin analog of this invention can be carried out in accordance with our copending PCT patent application, attorney reference wpp83894, which also claims priority from the PCT filing published as WO 0069862 published 23 November 2000, and which relates to hemisynthetic methods and new compounds. We incorporate the text of the copending PCT application, attorney reference wpp83894, by reference to the extent that there is disclosure therein which is not in the present specification.

Typically the hemisynthesis of an analog of this invention involves:

a) conversion if necessary of a quinone system for the ring *E* into the phenol system

b) conversion if necessary of a quinone system for the ring *A* into the phenol system;

c) conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring; and

d) derivatisation as appropriate, such as acylation.

Step (a), conversion if necessary of a quinone system for the ring *E* into the phenol system, can be effected by conventional reduction procedures. A suitable reagent system is hydrogen with a palladium-carbon catalyst, though other reducing systems can be employed.

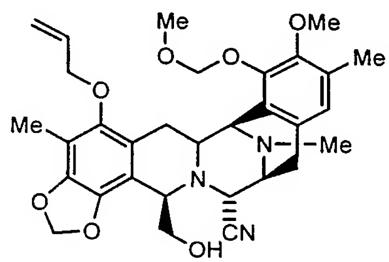
Step (b), conversion if necessary of a quinone system for the ring *A* into the phenol system is analogous to step (a), and more detail is not needed.

Step (c), conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring, can be effected in several ways, possibly along with step (b). For example, a quinone ring A can be demethylated in the methoxy substituent at the 7-

position and reduced to a dihydroquinone and trapped with a suitable electrophilic reagent such as CH_2Br_2, $BrCH_2Cl$, or a similar divalent reagent directly yielding the methylenedioxy ring system, or with a divalent reagent such as thiocarbonyldiimidazol which yields a substituted methylenedioxy ring system which can be converted to the desired ring.

Derivatisation in step (d) can include acylation, for instance with a group R^a-CO- as well as conversion of the 12-NCH_3 group to 12-NH or 12-NCH_2CH_3. Such conversion can be effected before or after the other steps, using available methods.

By way of illustration, it is now feasible to transform cyanosafracin B in a shorter and more straightforward way to make new analogs. Cyanosafracin B can be transformed into Intermediate **25**;



INT-25

and from this derivative it is possible to introduce further analogs of this invention.

One method of this invention transforms cyanosafracin B into intermediate **25** through a sequence of reactions that involves essentially (1) removal of methoxy group placed in ring A, (2) reduction of ring A and formation of methylene-dioxy group in one pot, (3) hydrolysis of amide function placed over carbon 1, (4) transformation of the resulting amine group into hydroxyl group.

The conversion of the **2**-cyano compound into Intermediate **25** usually involves the following steps (see scheme II):

formation of the protected compound of Formula **14** by reacting **2** with *tert*-butoxycarbonyl anhydride;

converting of **14** into the di-protected compound of Formula **15** by reacting with bromomethylmethyl ether and diisopropylethylamine in acetonitrile;

selectively elimination of the methoxy group of the quinone system in **15** to obtain the compound of Formula **16** by reacting with a methanolic solution of sodium hydroxide;

transforming of **16** into the methylene-dioxy compound of Formula **18** by employing the next preferred sequence: (1) quinone group of compound **16** is reduced with 10% Pd/C under hydrogen atmosphere; (2) the hydroquinone intermediate is converted into the methylenedioxy compound of Formula **17** by reacting with bromochloromethane and caesium carbonate under hydrogen atmosphere; (3) **17** is transformed into the compound of Formula **18** by protecting the free hydroxyl group as a OCH_2R group. This reaction is carried out with $BrCH_2R$ and caesium carbonate, where R can be aryl, $CH=CH_2$, OR′ etc.

elimination of the *tert*-butoxycarbonyl and the methyloxymethyl protecting groups of **18** to afford the compound of Formula **19** by reacting with a solution of HCl in dioxane. Also this reaction is achieved by mixing **18** with a solution of trifluoroacetic acid in dichloromethane;

formation of the thiourea compound of Formula **20** by reacting **19** with phenylisothiocyanate;

converting compound of Formula **20** into the amine compound of Formula **21** by reacting with a solution of hydrogen chloride in dioxane;

transforming compound of Formula **21** into the *N*-Troc derivative **22** by reacting with trichloroethyl chloroformate and pyridine;

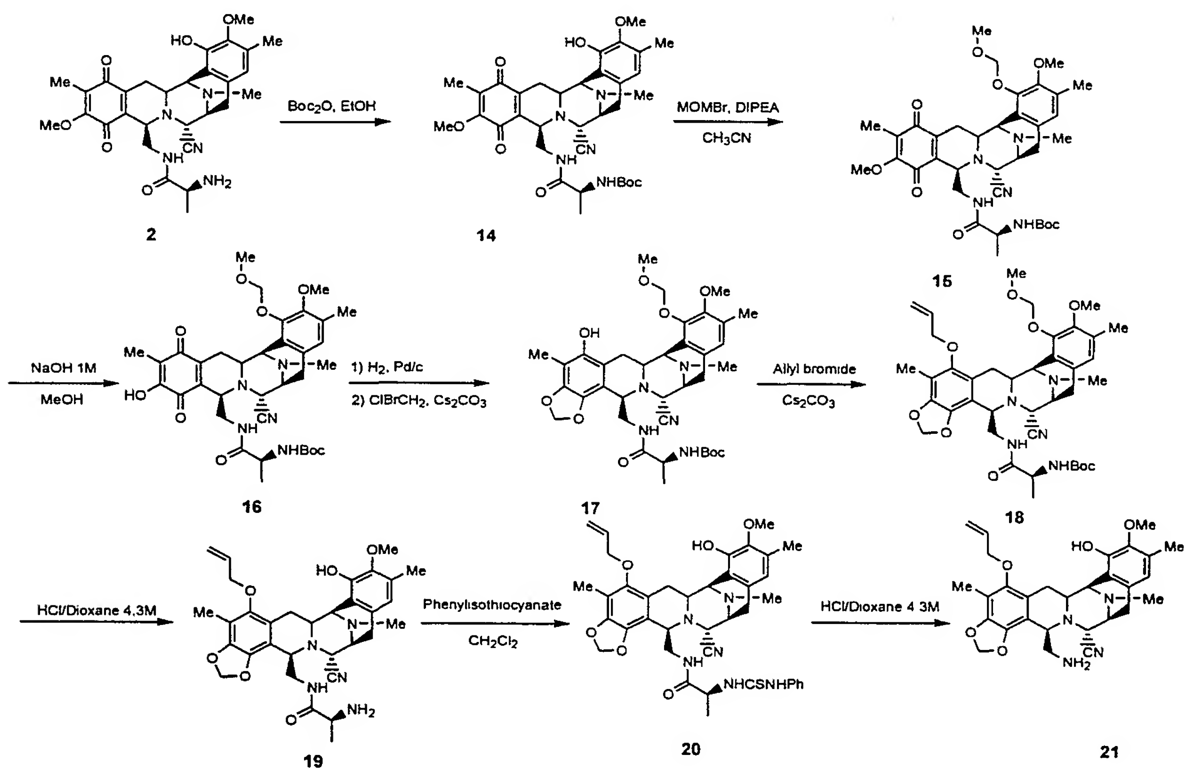
formation of the protected hydroxy compound of Formula **23** by reacting **22** with bromomethylmethyl ether and diisopropylethylamine;

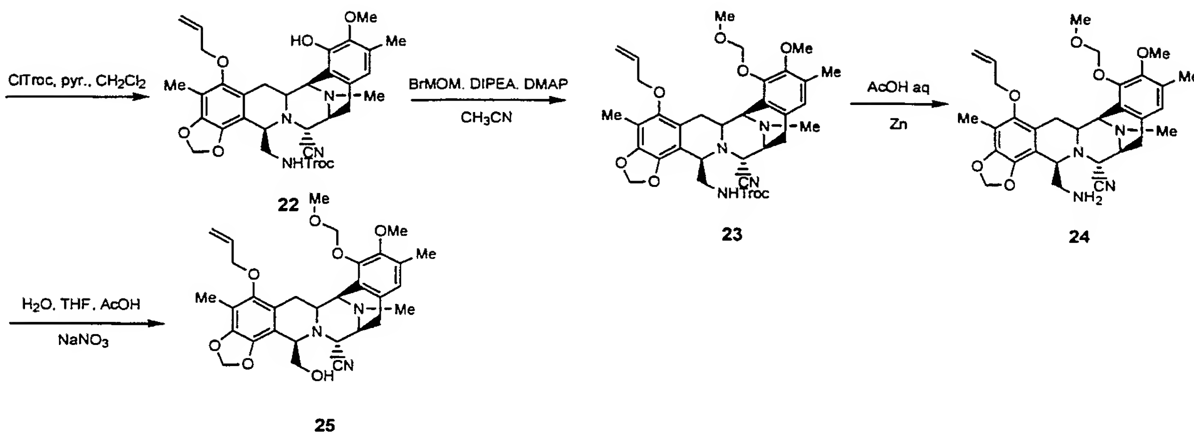
transforming compound of Formula **23** into the *N*-H derivative **24** by reacting with acetic

acid and zinc;

conversion of compound of Formula **24** into the hydroxy compound of Formula **25** by reaction with sodium nitrite in acetic acid. Alternatively, it can be used nitrogen tetroxide in a mixture of acetic acid and acetonitrile followed by treatment with sodium hydroxide. Also, it can be used sodium nitrite in a mixture of acetic anhydride-acetic acid, followed by treatment with sodium hydroxide.

Scheme II

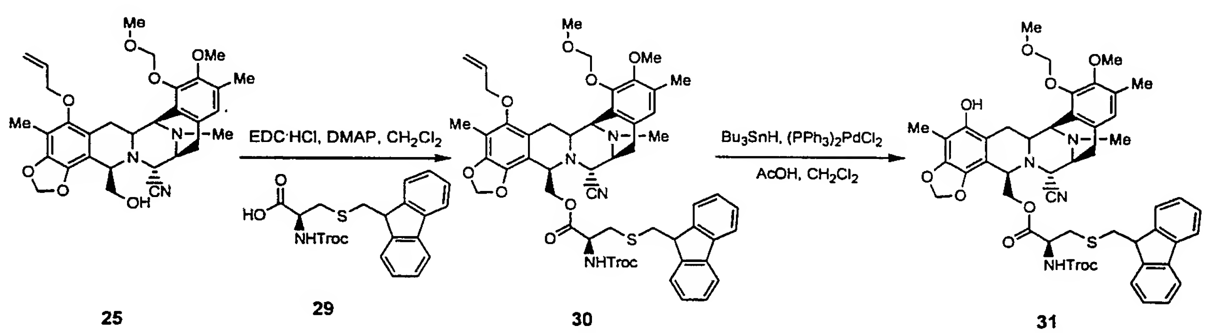




The conversion of the Intermediate **25** compound into other analogs of this invention is then readily achieved, as illustrated for example in Scheme III, which usually involves the following steps:

transforming compound of formula **24** into the derivative **30** by protecting the primary hydroxyl function with (S)-N-2,2,2-tricloroethoxycarbonyl-S-(9H-fluoren-9-ylmethyl)cysteine **29**;

converting the protected compound of formula **30** into the phenol derivative **31** by cleavage of the allyl group with tributyltin hydride and dichloropalladium-bis (triphenylphosphine). transforming the phenol compound of Formula **31** into compound of formula **32** by oxidation with benzeneseleninic anhydride at low temperature;



The route described above to transform Intermediate **25** can be conveniently modified to form other derivatives.

In more detail, the conversion of the starting 21-cyano compound to a related product of this invention, such as one of formula (XX), usually involves the following steps:

a) conversion if necessary of a quinone system for the ring *E* into the phenol system
b) formation of the -R^5 group at the 5-position in ring *A*;
c) formation of the R^1 group at the 1-position in ring *B*; and
d) conversion if necessary of a quinone system for the ring *A* into the phenol system;
e) conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring.

These steps have many similarities with the steps given previously. Step (c) typically involves forming a group -CH_2NH_2 at the 1-position and acylating it.

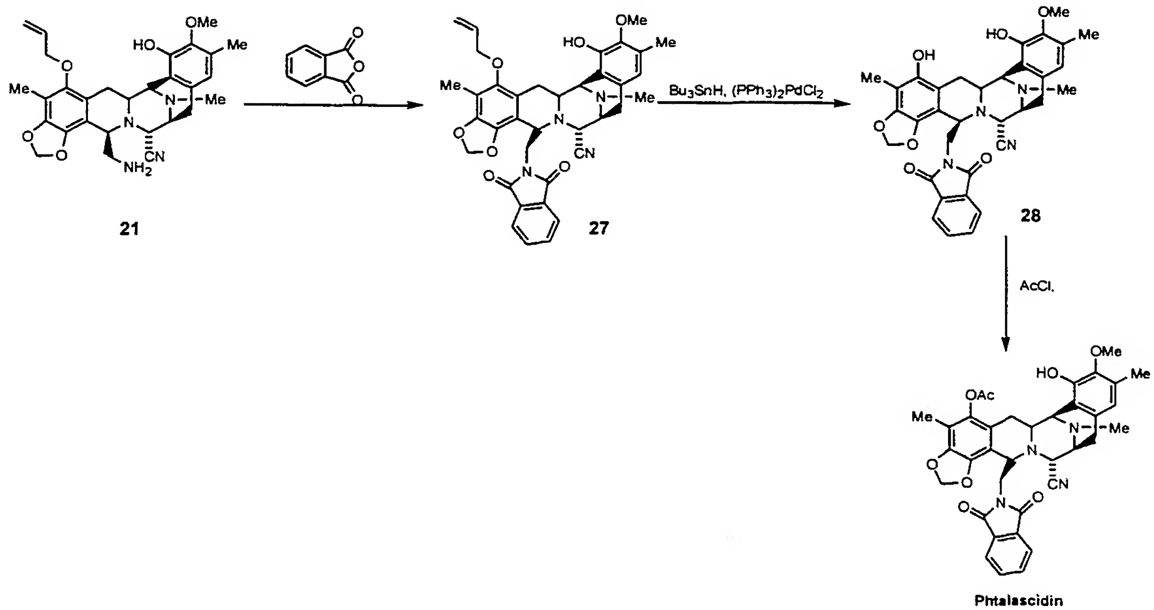
Phthlascidin can be made using Intermediates described in the conversion of cyanosafracin B into Intermediate **25**. For example, Intermediates **21** and **17** are suitable starting materials to make Phthlascidin and other analogs of this invention.

As shown in scheme V, the process for the synthetic formation of phthlascidin starting from Intermediate **21** comprises the sequential steps of:

transforming of **21** into the compound of Formula **27** by reaction with phthalic anhydride in dichloromethane and carbonyldiimidazole.

converting of **27** into phthlascidin by reacting with tributyltin hydride and dichloro palladium-bis(triphenylphosphine) or basic media, followed by reaction with acetyl chloride.

Scheme V



As shown in scheme VI, the process for the synthetic formation of phthlascidin starting from Intermediate **17** comprises the sequential steps of:

acetylation of the hydroxyl group of compound of formula **17** with acetyl chloride and pyridine to give the acetylated intermediate compound of formula **42**;

removal of the *tert*-butoxycarbonyl and the methyloxymethyl protecting groups of **42** to afford the compound of Formula **43** by reacting with a solution of HCl in dioxane. Also this reaction is achieved by mixing **42** with a solution of trifluoroacetic acid in dichloromethane;

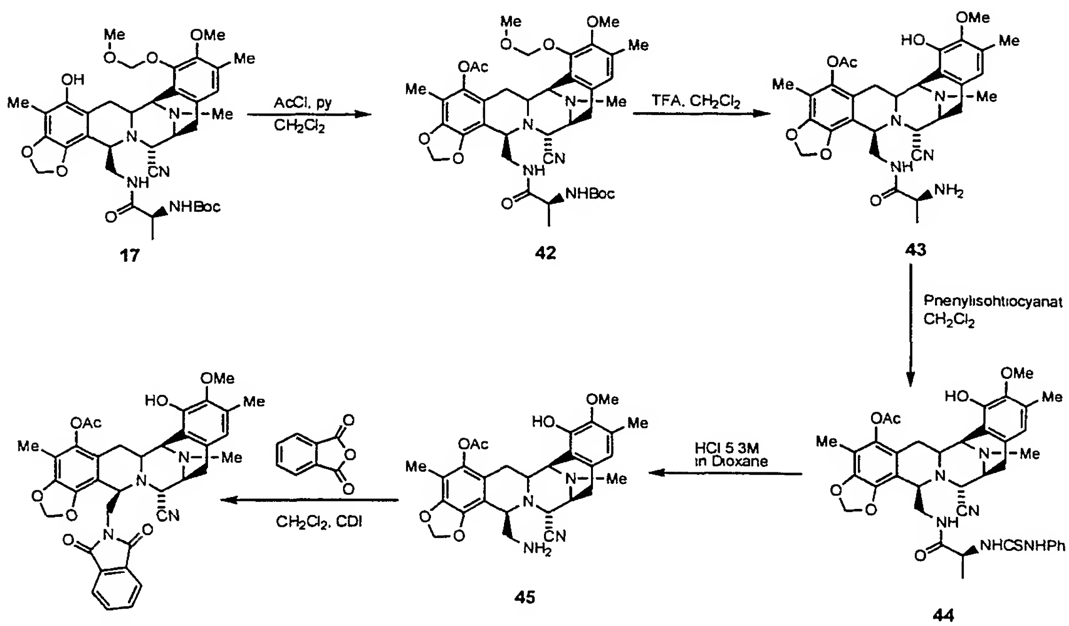
formation of the thiourea compound of Formula **44** by reacting **43** with phenylisothiocyanate;

converting compound of Formula **44** into the amine compound of Formula **45** by reacting with a solution of hydrogen chloride in dioxane;

transforming of **45** into phthlascidin by reaction with phthalic anhydride in dichloromethane and carbonyldiimidazole.

Other analogs can be made for example from **43** or **45** by a similar manner.

Scheme VI



The conversion of the 21-cyano compound to Intermediate 11 or a related intermediate of formula (XXI) usually involves the following steps:

a) conversion if necessary of a quinone system for the ring *E* into the phenol system

b) formation of the -OProt[1] group at the 18-position, in ring *E*;

c) formation of the -CH_2-OProt[2] group at the 1-position, in ring *B*; and

d) conversion if necessary of a quinone system for the ring *A* into the phenol system;

e) conversion of the phenol system for the ring *A* into the methylenedioxyphenol ring.

Step (b), formation of the -OProt[1] group at the 18-position in ring *E*, is a typical protection reaction for a phenol group, and no special comments need to be made. Appropriate conditions are chosen depending on the nature of the protecting group. The other steps are similar to the other reactions.

Step (b), formation of the -CH_2-OProt[2] group at the 1-position in ring *B*, is normally

carried out by forming a group $-CH_2NH_2$ at the 1-position and then converting the amine function to a hydroxy function and protecting. Thus, where the starting material has a group R^1 which is $-CH_2-NH-CO-CR^{25a}R^{25b}R^{25c}$ then it is matter of removing the N-acyl group. Where the starting material has a group R^1 which is $-CH_2-O-CO-R$ then no change may be needed for an ecteinascidin product where the substituent R^1 is the same. For other products, it is matter of removing the O-acyl group. Various procedures are available for such de-acylations. In one variation, the deacylation and conversion to a hydroxy function are performed in one step. Thereafter, the hydroxy group can be acylated or otherwise converted to give the appropriate R^1 group.

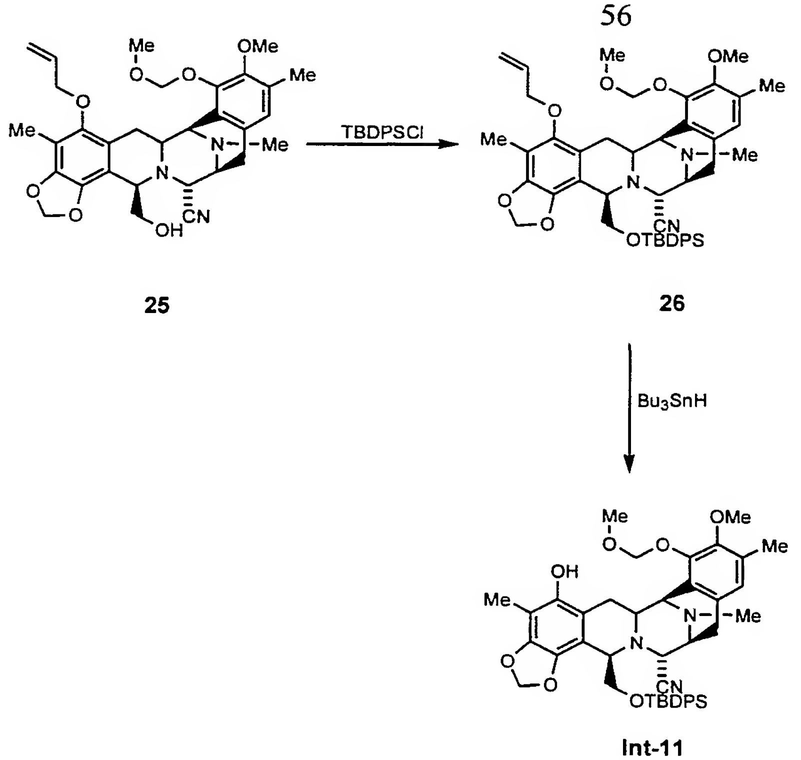
U.S. Patent N° 5,721,362 describe synthetic methods to make ET-743 through a long multistep synthesis. One of the Intermediates of this synthesis is Intermediate 11. Using cyanosafracin B as starting material it is possible to reach Intermediate 11 providing a much shorter way to make such Intermediate and therefor improving the method to make ET-743

Cyanosafracin B can be converted into Intermediate **25** by the methods described above. From Intermediate **25** is possible to reach Intermediate 11 using the following steps, see scheme VII.

formation of the protected hydroxy compound of Formula **26** by reacting **25** with *tert*-butyldiphenylsilyl chloride in the presence of a base;

final cleavage of the allyl group with tributyltin hydride and dichloropalladium-bis (triphenylphosphine) in **26** that leads to the formation of the intermediate **11.**

Scheme VII



One embodiment of the synthetic process of the present invention to transform safracin B into intermediate **11** is a modification and extension of Scheme VIII and comprises the sequential steps of:

stereospecifically converting the compound Safracin B to the compound of Formula **2** by selective replacement of OH by CN by reacting with KCN in acid media;

forming the thiourea compound of Formula **3** by reacting compound of Formula **2** with phenyl isothiocyanate;

converting the thiourea compound of Formula **3** into the acetamide of Formula **5** by an hydrolysis in acid media followed by addition of acetic anhydride; The intermediate amine compound of Formula **4** can be isolated by quenching the hydrolysis in acid media with sodium bicarbonate, but this intermediate is highly unstable, and is transformed quickly into a five member cyclic imine, named compound **6**;

forming the protected compound of Formula **7** by reacting with bromomethylmethyl ether and diisopropylethylamine in dichloromethane;

selectively de-methylating the methoxy group of the quinone system of compound of Formula **7** into the compound of Formula **8** by reacting with methanolic solution of sodium hydroxide;

transforming the compound of Formula **8** into methylenedioxy-compound of Formula **9** by the preferred following sequence: (1) quinone group of compound **8** is reduced with 10% Pd/C under hydrogen atmosphere; (2) the hydroquinone intermediate is converted into the methylene-dioxy compound of Formula **9** by reacting with bromochloromethane and cesium carbonate under hydrogen atmosphere; (3) compound of Formula **9** is transformed into compound of Formula **10** by protecting the free hydroxyl group as a OCH_2R group, by reacting with $BrCH_2R$ and cesium carbonate, where R can be aryl, $CH{=}CH_2$, OR′ etc.;
converting the acetamide group of compound of Formula **10** into the corresponding hydroxyl group of Formula **11** by reaction with nitrogen tetroxide in a mixture of acetic acid and acetic acetate followed by treatment with sodium hydroxide; alternatively can be used sodium nitrite in a mixture of acetic anhydride acetic acid, followed by treatment with sodium hydroxide; alternatively the acetamide group of compound of Formula **10** can be converted into the primary amine group by reacting with hydrazine or with Boc_2O, DMAP followed by hydrazine; such primary amine can be converted into the corresponding hydroxyl group (compound of Formula **11**) by an oxidative conversion of the primary amine into the corresponding aldehyde with 4-formyl-1-methylpyridinium benzenesulphonate or other pyridinium ion, followed by DBU or other base treatment and further hydrolization, and followed by the reduction of the aldehyde to the corresponding hydroxyl group with lithium aluminium hydride or other reducing agent;
forming the protected compound of Formula **26** by reacting with t-butyldiphenylsilyl chloride and dimethylaminopyridine in dichloromethane;
transforming the silylated compound of Formula **26** into the intermediate **11** by deprotection of the OCH_2R protecting group, by reacting under reductive conditions or acid conditions. Typical procedures are with palladium black under hydrogen atmosphere, or aqueous TFA, or tributyltin hydride and dichlorobis (triphenylphosphine palladium).

In yet another preferred modification, the cyano compound of Formula **2** can be transformed into Intermediate **11** using an extension of the scheme II, involving the further steps of.
formation of the protected hydroxy compound of Formula **26** by reacting **25** with *tert*-butyldiphenylsilyl chloride in the presence of a base;
final cleavage of the allyl group with tributyltin hydride and dichloropalladium-bis

(triphenylphosphine) in **26** that leads to the formation of the intermediate **11.**

Thus, it is possible to transform cyanosafracin B into a number of intermediates and derivatives with potential antitumor therapeutic activity. These intermediates can be made starting from already described compounds, or using alternative routes.

Intermediates described herein comprise compound **47**, and a numbers of amide derivatives made using compounds **45** or **43.**

In Scheme VIII is described formation of compound **47** using the following sequence:

forming the thiourea compound of Formula **3** by reacting compound of Formula **2** with phenyl isothiocyanate;

converting the thiourea compound of Formula **3** into the acetamide of Formula **5** by an hydrolysis in acid media followed by addition of acetic anhydride; The intermediate amine compound of Formula **4** can be isolated by quenching the hydrolysis in acid media with sodium bicarbonate, but this intermediate is highly unstable, and is transformed quickly into a five member cyclic imine, named compound **6**;

forming the protected compound of Formula **7** by reacting with bromomethylmethyl ether and diisopropylethylamine in dichloromethane;

selectively de-methylating the methoxy group of the quinone system of compound of Formula **7** into the compound of Formula **8** by reacting with methanolic solution of sodium hydroxide;

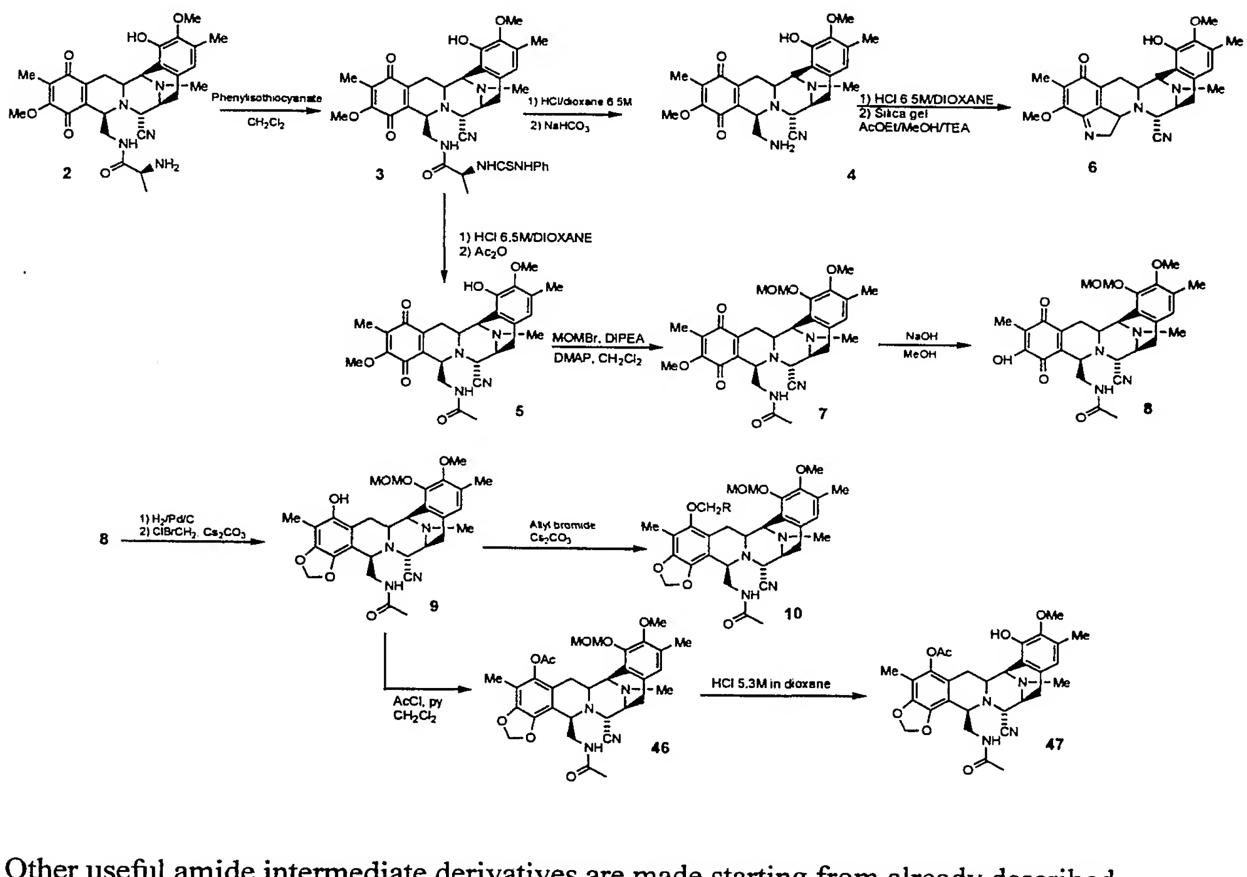
transforming the compound of Formula **8** into methylenedioxy-compound of Formula **10** by the preferred following sequence: (1) quinone group of compound **8** is reduced with 10% Pd/C under hydrogen atmosphere; (2) the hydroquinone intermediate is converted into the methylene-dioxy compound of Formula **9** by reacting with bromochloromethane and cesium carbonate under hydrogen atmosphere; (3) compound of Formula **9** is transformed into

compound of Formula **10** by protecting the free hydroxyl group as a allyloxy group, by reacting with allyl-bromide and cesium carbonate;

transforming the compound of formula **9** into acetyl-derivative **46** by reaction with acetyl chloride in pyridine;

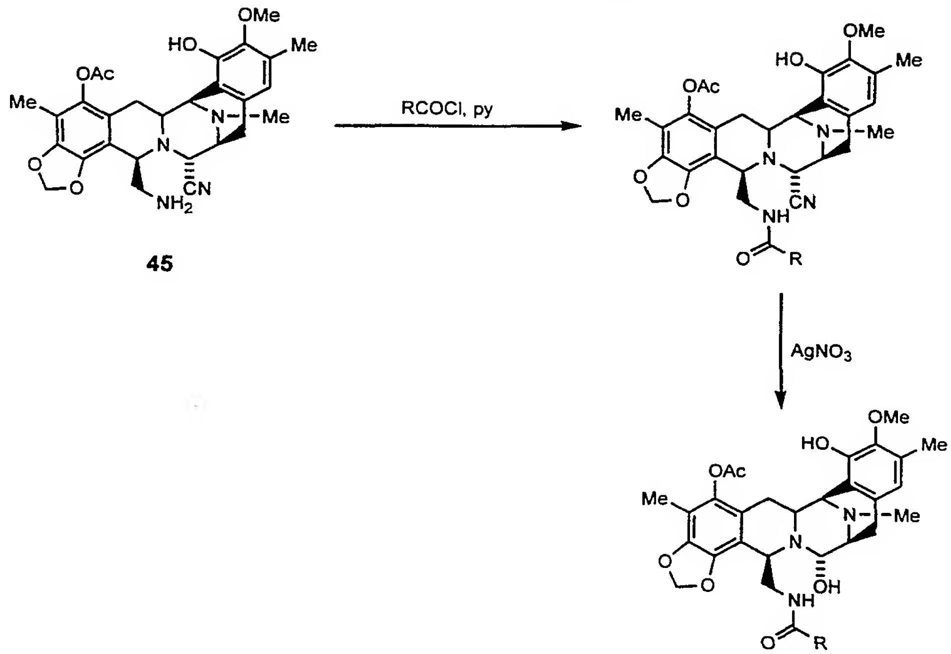
transforming compound of formula **46** into de-protected compound **47** by reaction with hydrochloric acid in dioxane.

Scheme VIII



Other useful amide intermediate derivatives are made starting from already described intermediate **45** using the next scheme:

Scheme IX



The second step is optional. This process is an important part of the invention, particularly where the group R is a group R^a as previously defined. Furthermore, the Scheme VIII can be readily broadened to enable preparation of compounds of formula (XXIII), by inclusion in the starting material of a different group at the 5-position, either a group directly intended for the product or a group which can be removed or otherwise modified to give the desired group.

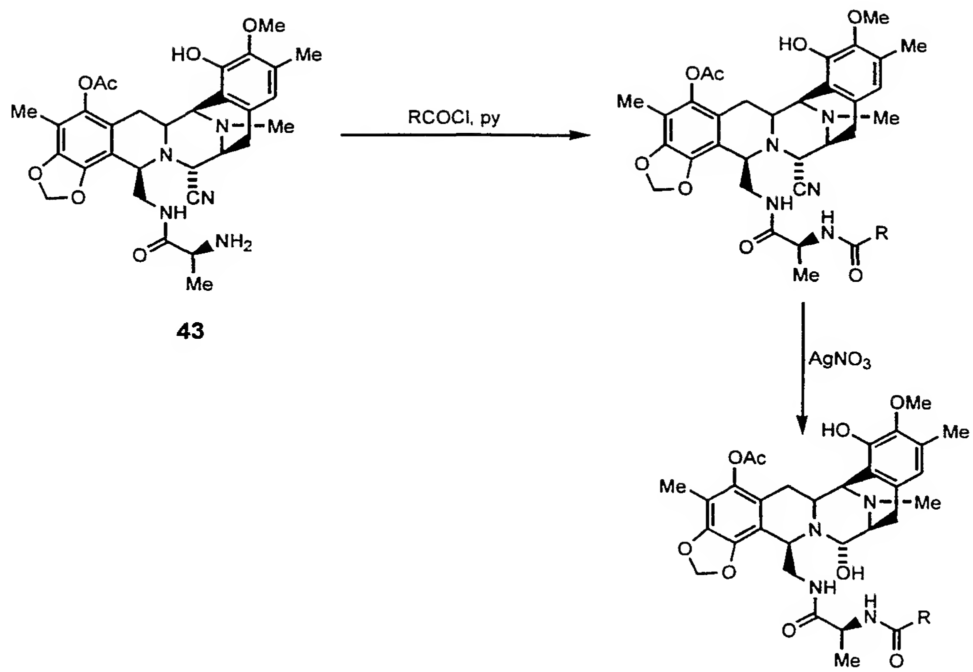
From compound **45** can be made a group of analogs through the following sequence:

acylation in the amino group of compound of Formula **45** by a wide range of acyl derivatives to provide the corresponding amides, where preferred acyl groups are acetyl, cinnamoyl chloride, p-trifluorocinnamoyl chloride, isovaleryl chloride phenylisothiocyanate or aminoacids, or the other examples previously given of groups R^aCO-.

transforming the CN group into an OH group by reaction with silver nitrate in a mixture AcN/H_2O.

Other useful amide intermediate derivatives are made starting from already described intermediate **43** using the next scheme:

Scheme X

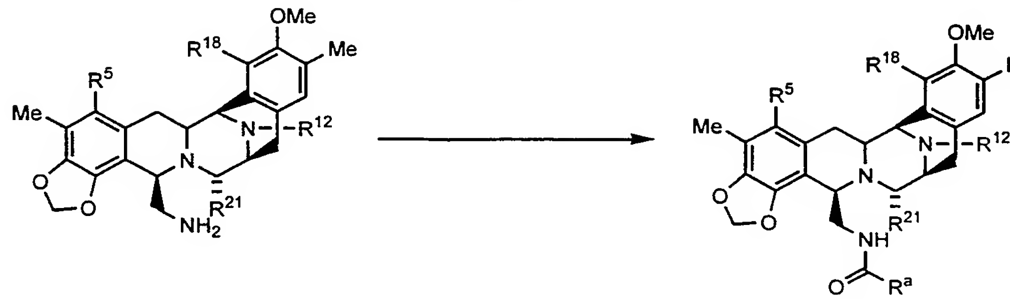


From Compound **43** can be obtained another group of interesting derivatives using the following sequence:

(a) acylation in the amino group of compound of Formula **43** by a wide range of acyl derivatives to provide the corresponding amides, where preferred acyl groups are acetyl, cinnamoyl chloride, p-trifluorocinnamoyl chloride, isovaleryl chloride or aminoacids, or the other examples previously given of groups R^aCO-.

(b) transforming the CN group into an OH group by reaction with silver nitrate in a mixture AcN/H_2O

Reflecting the active compounds, an important process in accordance with this invention is as follows:



where R^5 for the end product is as defined for the compound (XXII) and may be different in the starting material and converted thereto as part of the process,

R^{18} is a hydroxy group in the end product but may be a protected hydroxy group in the starting material and converted thereto as part of the process,

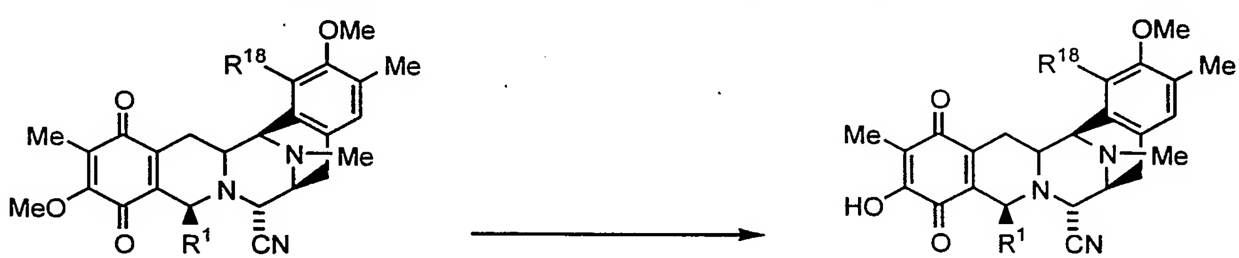
R^{12} for the end product may be the same as in the starting material or may be converted thereto as part of the process,

R^{21} for the end product is as defined and if a hydroxy group may be formed from a cyano group as part of the process,

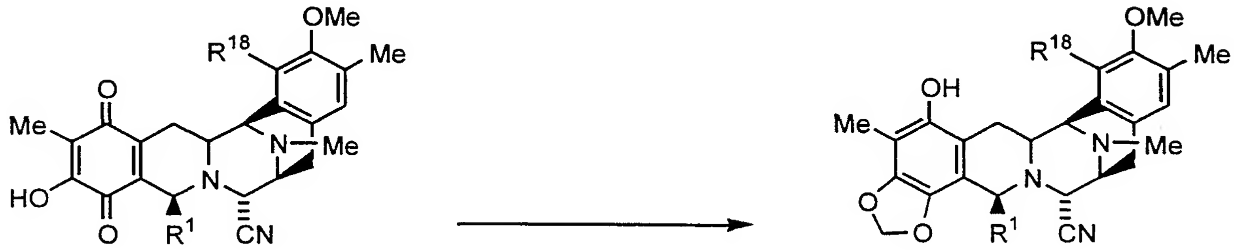
R^a is as defined, and may be further acylated as part of the process to give an end product with an acylated R^a group as discussed.

R^5 is preferably oxyacetyl or other small oxyacyl group in the starting material and is not changed in the reaction. R^{18} is preferably a hydroxy group in the starting material and is not changed in the reaction. R^{12} is preferably $-NCH_3-$ in the starting material and is not changed in the reaction. R^{21} the end product is as defined and if a hydroxy group may be formed from a cyano group as part of the process. R^a is in the final product is preferably as defined in relation to the compound of formula (XXIII).

Another important method of this invention includes the reaction:

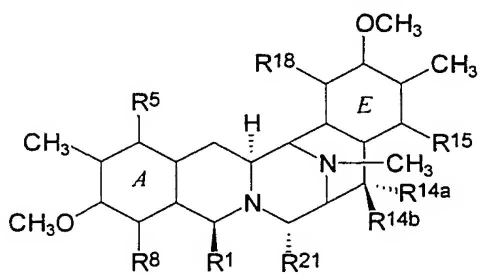


Another important method of this invention includes the reaction:



Another important method of this invention includes the reaction includes the reaction where a group R^1 is aminomethylene is converted to a hydroxymethylene group.

Another important method of this invention includes the reaction for preparing a 21-cyano compound of formula (XVI) which comprises reacting a compound of formula (XV):



where R^1, R^5, R^8, R^{14a}, R^{14b}, R^{15} and R^{18} are as defined and R^{21} is a hydroxy group, with a source of cyanide ion, to give the desired 21-cyano compound.

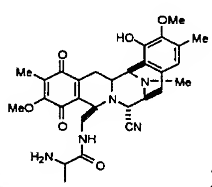
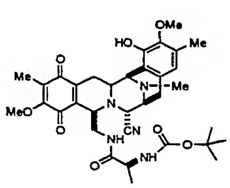
In addition, processes using other nucleophile-containing compounds, to produce similar compounds of formula (XVI) wherein the 21-position is protected by another nucleophilic group, a 21-Nuc group, are also envisaged. For example, a 21-Nuc compound of formula (XVI) with an alkylamino substituent at the 21-position can be produced by reacting the compound of formula (XV) wherein R^{21} is a hydroxy group with a suitable alkylamine. A 21-Nuc compound of formula (XVI) with an alkylthio substituent at the 21-position can also be produced by reacting the compound of formula (XV) wherein R^{21} is a hydroxy group with a suitable alkanethiol. Alternatively, a 21-Nuc compound of formula (XVI) with an α-carbonylalkyl substituent at the 21-position can be produced by reacting the compound of formula (XV) wherein R^{21} is a hydroxy group with a suitable carbonyl compound, typically in the presence of a base. Other synthetic routes are available for other

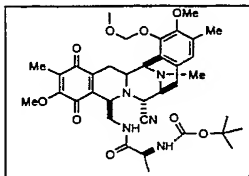
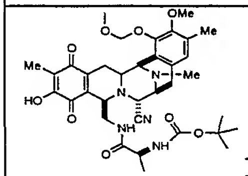
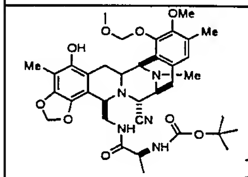
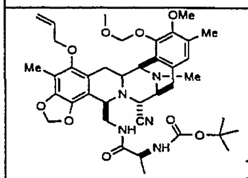
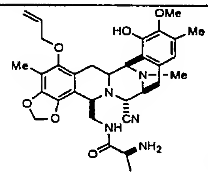
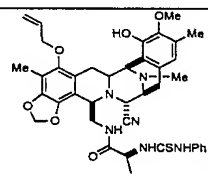
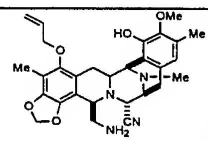
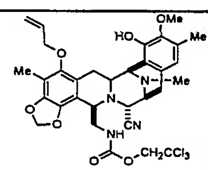
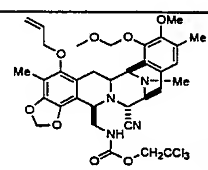
21-Nuc compounds.

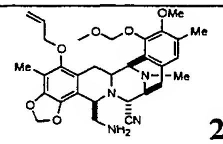
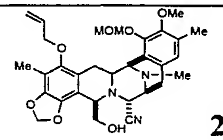
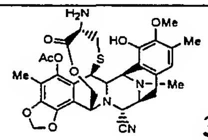
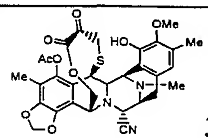
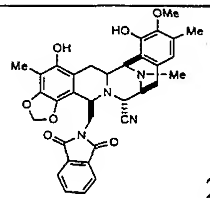
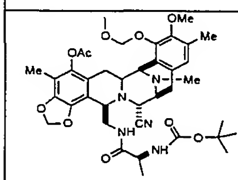
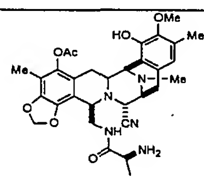
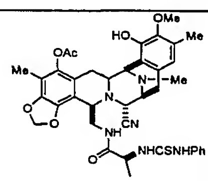
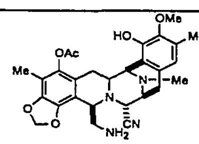
Another important reaction of this invention involves treatment of a 21-cyano product of this invention to form a 21-hydroxy compound. Such compounds have interesting *in vivo* properties.

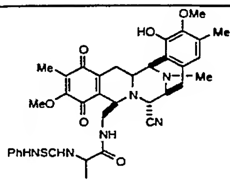
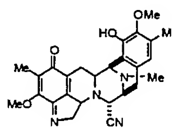
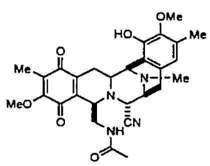
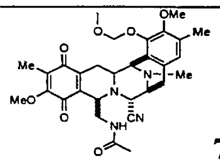
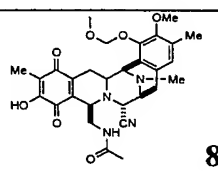
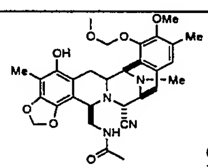
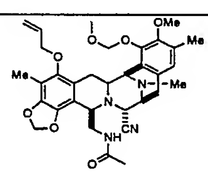
For the avoidance of doubt, the stereochemistries indicated in this patent specification are based on our understanding of the correct stereochemistry of the natural products. To the extent that an error is discovered in the assigned stereochemistry, then the appropriate correction needs to be made in the formulae given throughout in this patent specification. Furthermore, to the extent that the syntheses are capable of modification, this invention extends to stereoisomers.

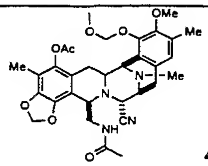
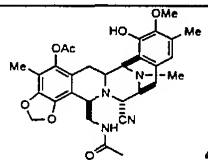
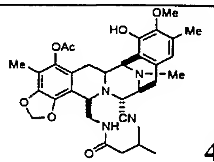
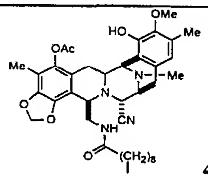
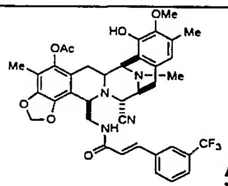
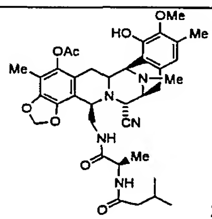
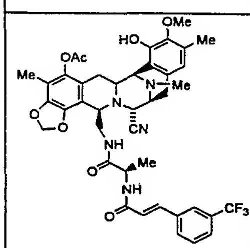
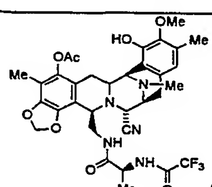
CYTOTOXIC ACTIVITIY

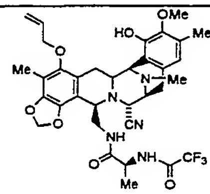
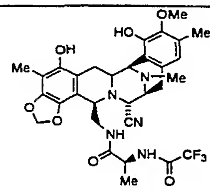
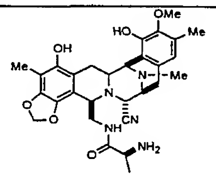
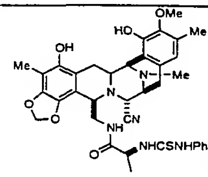
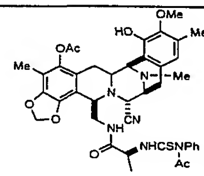
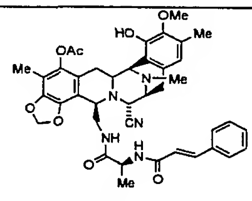
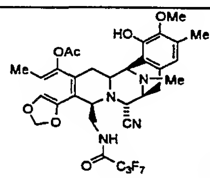
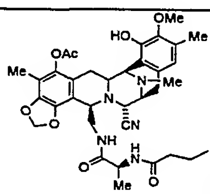
Compound	IC_{50} (μM)					
	P-388	A-549	HT-29	MEL-28	CV-1	DU-145
 2	0.009	0.018	0.018	0.018	0.023	
 14	0.15	>0.15	0.15	>0.15		

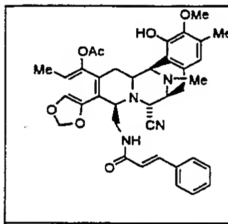
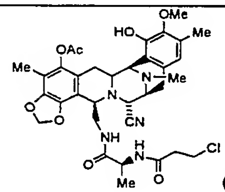
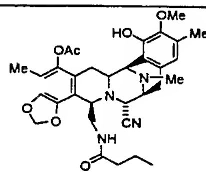
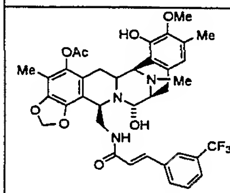
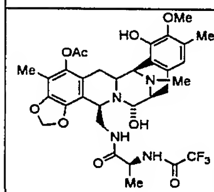
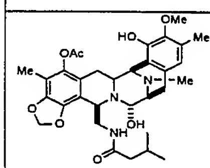
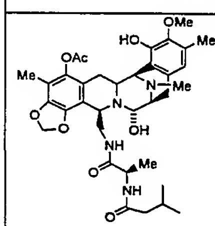
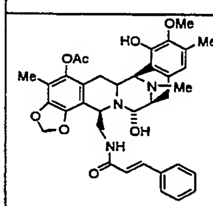
 15	1.44	1.44	1.44	1.44		
 16	>1.5	>1.5	>1.5	>1.5		
 17	1.4	1.4	1.4	1.4		
 18	0.01	0.01	0.01	0.01		
 19	0.08	0.16	0.01	0.16		
 20	0.01	0.01	0.01	0.01		
 21	0.019	0.019	0.019	0.019		
 22	0.014	0.014	0.014	0.014	0.014	0.014
 23	0.13	0.13	0.13	0.13	0.13	0.13

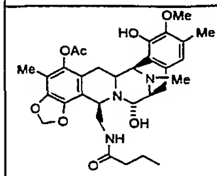
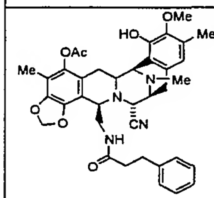
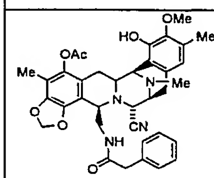
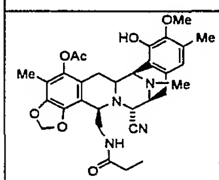
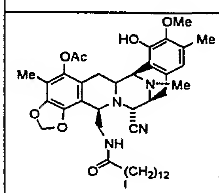
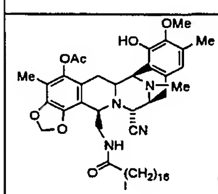
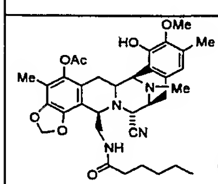
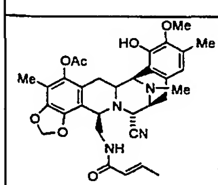
 24	0.18	1.8	1.8	1.8	1.8	1.8
 25	0.2	0.2	0.2	0.2		0.2
 35	0.008	0.008	0.008	0.008		
 36	0.01	0.01	0.01	0.01		
 28	0.001	0.001	0.001	0.001	0.001	0.001
 42	0.13	0.13	0.13	0.13		0.13
 43	0.008	0.016	0.008	0.008		0.016
 44	0.001	0.001	0.001	0.001		0.001
 45	0.01	0.01	0.01	0.01		0.01

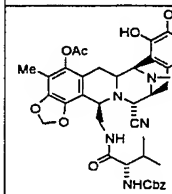
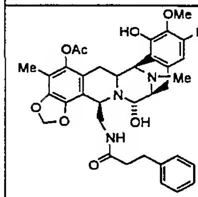
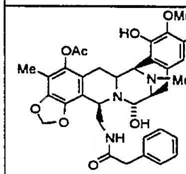
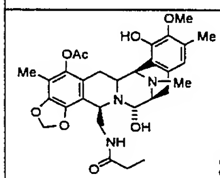
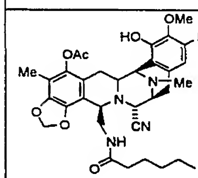
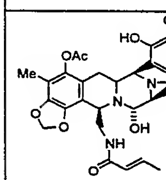
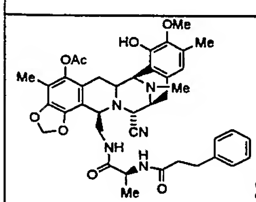
 3	0.015	0.015	0.015	0.015	0.018	
 6	2.171	2.171	2.171	2.171	2.171	
 5	0.005	0.005	0.005	0.005		
 7	0.22	0.22	0.22	0.22	0.22	
 8	>9	>18.1	>18.1	>18.1	>18.1	
 9	>1.77	>1.77	>1.77	>1.77		>1.77
 10	>1.65	>1.65	>1.65	>1.65		>1.65

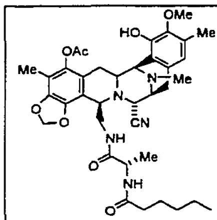
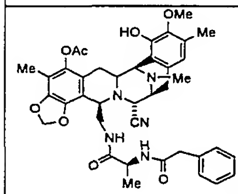
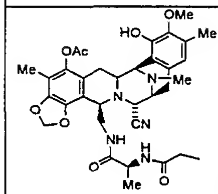
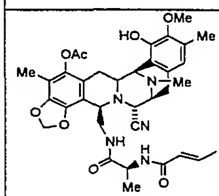
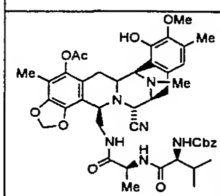
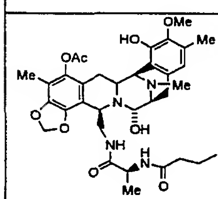
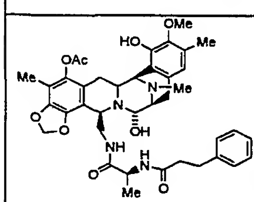
 46	0.016	0.016	0.016	0.016		0.016
 47	0.001	0.001	0.001	0.001		0.001
 48	0.0008	0.001	0.0008	0.0008		0.001
 49	0.007	0.007	0.007	0.007		0.007
 50	0.0001	0.0001	0.0001	0.0001		0.0001
 51	0.0001	0.0001	0.0001	0.0001		0.0001
 5 2	0.001	0.001	0.001	0.001		0.001
 53	0.0001	0.0001	0.0001	0.0001		0.0001

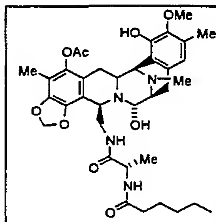
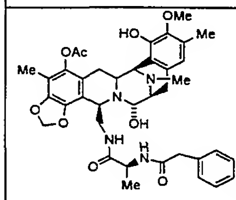
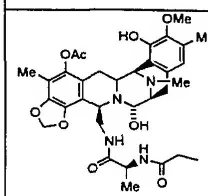
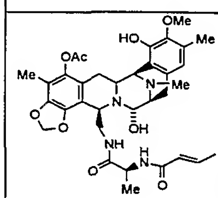
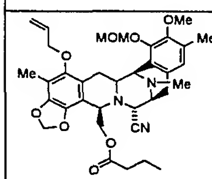
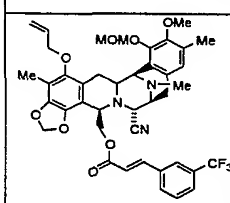
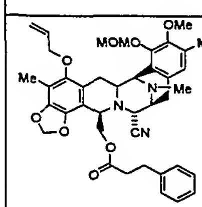
 54	0.001	0.001	0.001	0.001		0.001
 55	0.01	0.01	0.01	0.01		0.01
 56	0.18	0.9	0.18	0.8		0.9
 57	0.14	0.14	0.14	0.14		0.14
 58	0.001	0.001	0.001	0.001		0.001
 60	0.001	0.001	0.0001	0.001		0.0005
 61	0.001	0.001	0.001	0.001		0.001
 62	0.001	0.001		0.0005		0.001

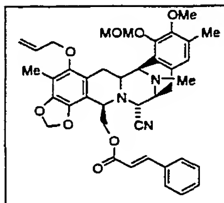
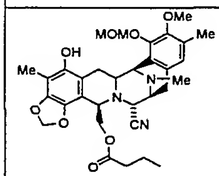
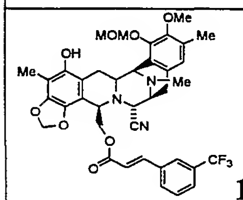
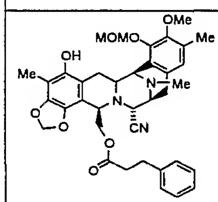
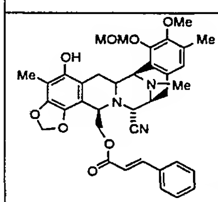
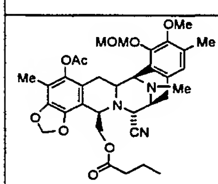
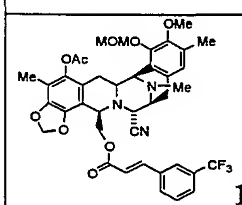
 63	0.0001	0.0001	0.0001	0.0001		0.0001
 64	0.001	0.001		0.001		0.001
 65	0.0001	0.0001	0.0001	0.0001		0.0001
 66	0.0001	0.0001	0.0001	0.0001		0.0001
 67	0.0001	0.0001	0.0001	0.0001		0.0001
 68	0.0008	0.001	0.0008	0.0008		0.001
 69	0.001	0.001	0.001	0.001		0.001
 70	0.0001	0.0001	0.0001	0.0001		0.0001

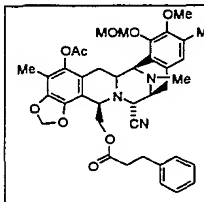
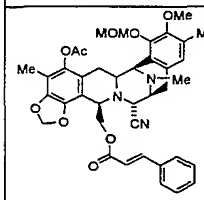
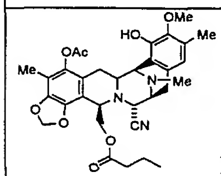
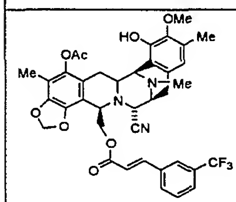
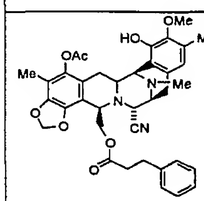
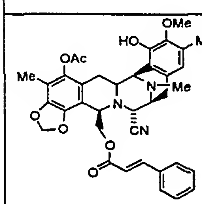
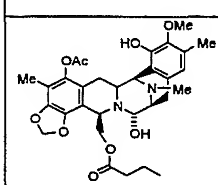
 **71**	0.0008	0.0008	0.0001	0.0008		0.0001
 **72**	0.0001	0.0001	0.0001	0.0001		0.0001
 **73**	0.0001	0.0001	0.0001	0.0001		0.0001
 **74**	0.0001	0.0001	0.0001	0.0001		0.0001
 **75**	0.1	0.1	0.1	0.1		0.1
 **76**	0.1	0.1	0.1	0.1		0.1
 **77**	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
 **78**	0.0001	0.0008	0.0001	0.0001		0.0008

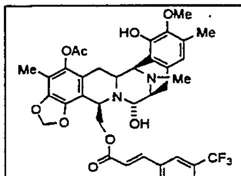
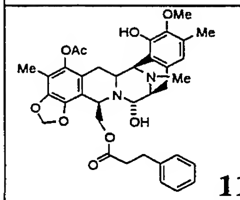
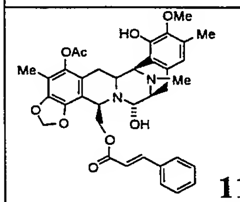
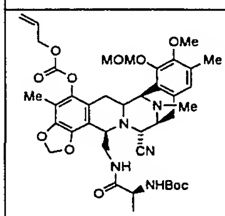
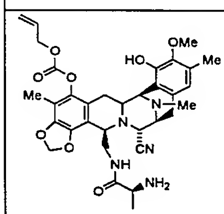
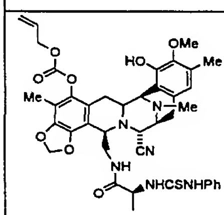
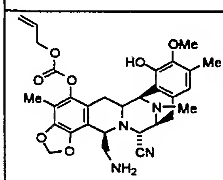
 **79**	0.001	0.001	0.001	0.001		0.001
 **80**	0.0001	0.0001	0.0001	0.0001		0.0001
 **81**	0.0007	0.0007	0.0007	0.0007		0.0007
 **82**	0.0001	0.0001	0.0001	0.0001		0.0001
 **83**	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
 **84**	0.0001	0.0008	0.0001	0.0001		0.0008
 **8** **5**	0.0006	0.001	0.0006	0.001		0.0006

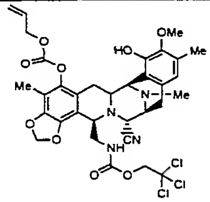
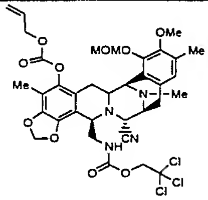
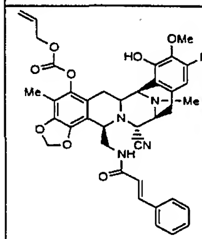
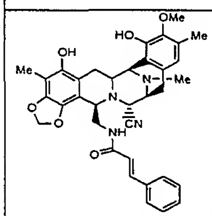
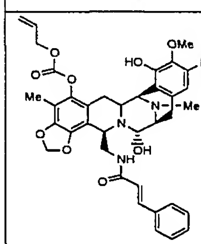
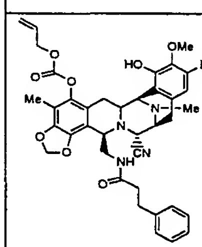
 86	0.001	0.001	0.001	0.001	0.001	0.001
 87	0.0001	0.0001	0.0001	0.0001		0.0001
 88	0.0007	0.0007	0.0007	0.0007		0.0007
 89	0.001	0.007	0.001	0.001		0.007
 90	0.01	0.01	0.01	0.01		0.01
 91	0.001	0.001	0.001	0.001		0.001
 9 2	0.0001	0.0001	0.0001	0.0001		0.0001

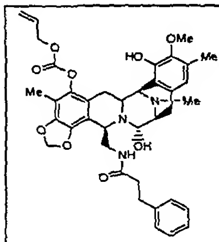
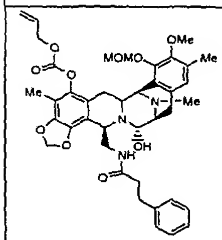
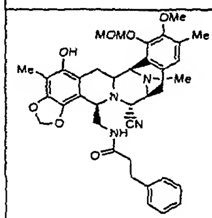
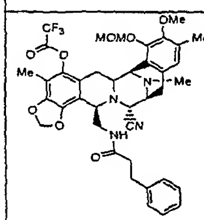
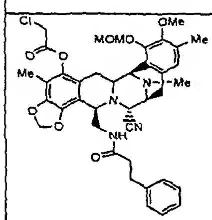
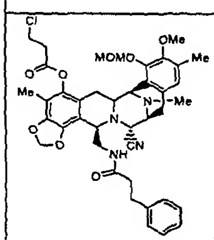
 93	0.001	0.001	0.001	0.001	0.001	0.001
 94	0.0007	0.0007	0.0007	0.0007		0.0007
 95	0.0001	0.0001	0.0001	0.0001		0.0001
 96	0.001	0.007	0.001	0.001		0.007
 97	>1	>1	>1	>1		>1
 98	>1	>1	>1	>1		>1
 99	0.7	0.7	0.7	0.7	0.7	0.7

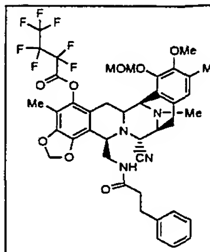
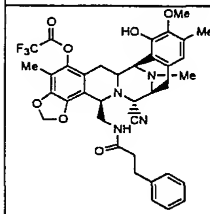
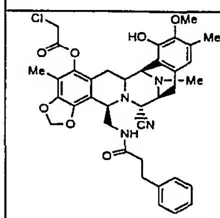
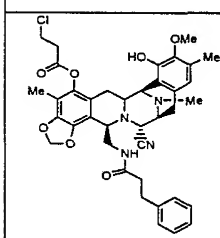
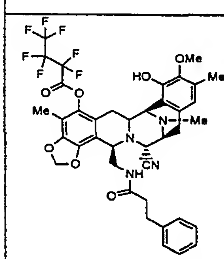
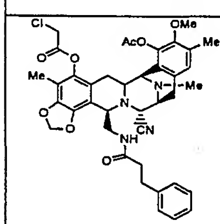
 100	0.1	0.1	0.1	0.1		0.1
 101	0.1	0.1	0.1	0.1		0.1
 102	0.1	0.1	0.1	0.1		0.1
 103	0.1	0.1	0.1	0.1		0.1
 104	0.1	0.1	0.1	0.1		0.1
 105	0.1	0.1	0.1	0.1		0.1
 106	0.6	0.6	0.6	0.6		0.6

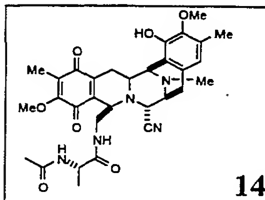
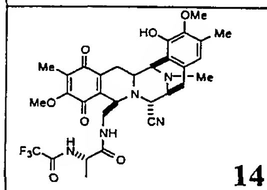
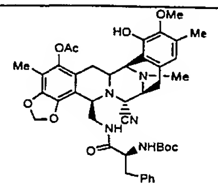
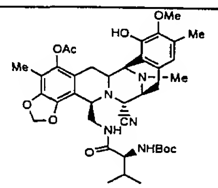
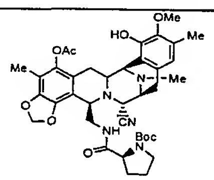
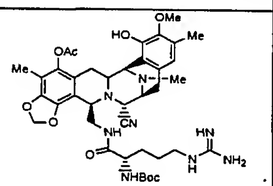
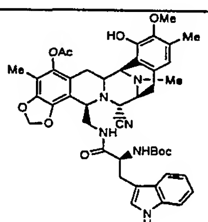
 **107**	0.1	0.1	0.1	0.1		0.1
 **108**	0.01	0.07	0.07	0.07		0.07
 **109**	0.0001	0.0008	0.0008	0.0008		0.0008
 **110**	0.001	0.001	0.001	0.001		0.001
 **111**	0.0001	0.0001	0.0001	0.0001		0.0001
 **112**	0.0007	0.0007	0.0007	0.0007		0.0007
 **113**	0.0001	0.0001	0.0001	0.0001		0.0001

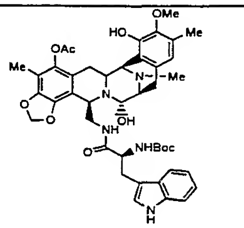
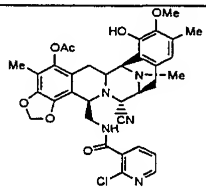
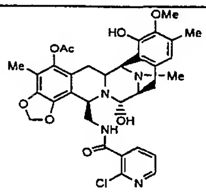
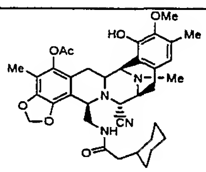
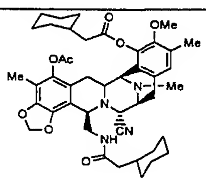
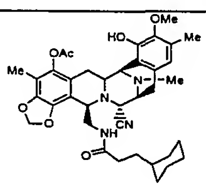
 114	0.0001	0.0001	0.0001	0.0001		0.0001
 115	0.0001	0.0001	0.0001	0.0001		0.0001
 116	0.0001	0.0007	0.0007	0.0007		0.0007
 117	0.06	0.06	0.06	0.06		0.06
 118	0.001	0.001	0.001	0.001		0.001
 119	0.001	0.001	0.001	0.001		0.001
 120	0.06	0.06	0.06	0.06		0.06

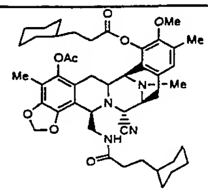
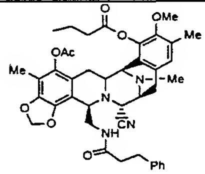
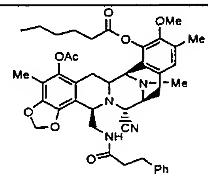
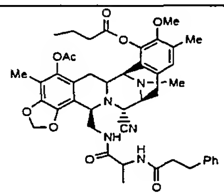
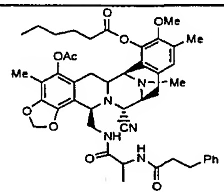
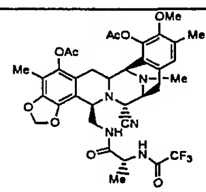
 **121**	0.006	0.006	0.006	0.006		0.006
 **122**	0.1	0.1	0.1	0.1		0.1
 **124**	0.0001	0.0001	0.0001	0.0001		0.0001
 **125**	0.001	0.001	0.001	0.001		0.001
 **126**	0.0001	0.0001	0.0001	0.0001		0.0001
 **127**	0.0001	0.0001	0.0001	0.0001		0.0001

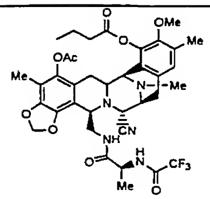
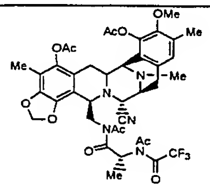
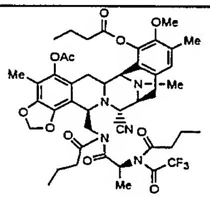
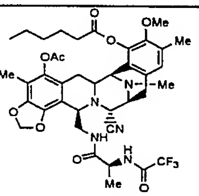
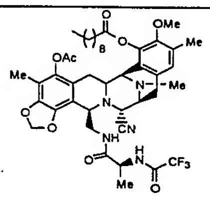
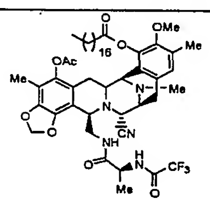
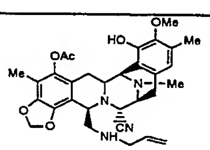
 128	0.0001	0.0001	0.0001	0.0001		0.0001
 129	0.1	0.1	0.1	0.1		0.1
 130	0.1	0.1	0.1	0.1		0.1
 131	0.5	0.5	0.5	0.5		0.5
 132	0.1	0.1	0.1	0.1		0.1
 133	0.05	0.05	0.05	0.05		0.05

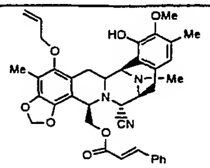
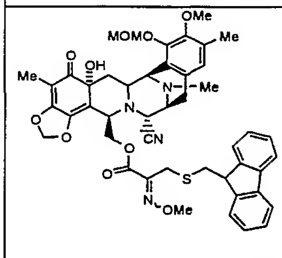
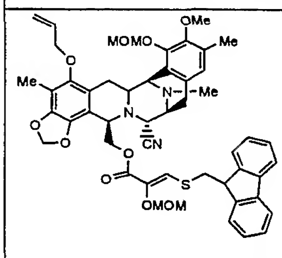
 **134**	0.5	0.5	0.5	0.5	0.5	0.5
 **135**	0.01	0.01	0.01	0.01		0.01
 **136**	0.001	0.001	0.001	0.001		0.001
 **137**	0.01	0.01	0.01	0.01		0.01
 **138**	0.006	0.006	0.006	0.006		0.006
 **139**	0.01	0.01	0.01	0.01		0.01

 **140**	0.08	0.08	0.08	0.08		0.08
 **141**	0.01	0.01	0.01	0.01	0.01	0.01
 **174**		0.0013	0.0013			
 **175**		0.007	0.007			
 **176**		0.014	0.014			
 **177**		>1	>1			
 **178**		0.00012	0.00012			

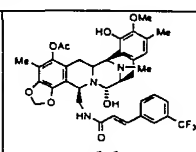
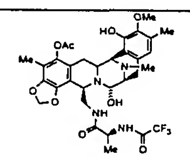
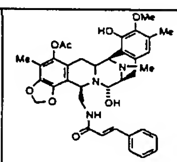
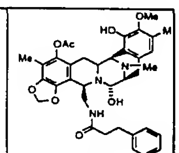
 **179**		0.012	0.012			
 **180**		0.00015	0.00015			
 **181**		0.00015	0.00015			
 **182**		0.0015	0.0015			
 **183**		0.013	0.013			
 **184**		0.0015	0.0015			

 **185**		0.12	0.12			
 **186**		0.0014	0.0014			
 **187**		0.013	0.013			
 **188**		0.012	0.012			
 **189**		0.06	0.06			
 **190**		0.013	0.013			

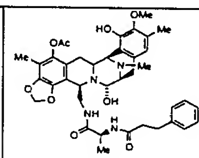
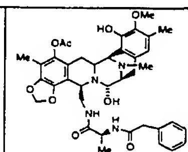
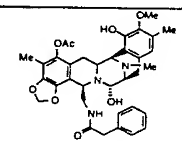
 **191**		0.13	0.13			
 **192**		0.12	0.12			
 **193**		0.11	0.11			
 **194**		0.012	0.012			
 **195**		0.012	0.012			
 **196**		0.1	0.1			
		0.0018	0.0018			

197						
 **198**		0.0015	0.0015			
 **199**		>1	>1			
 **202**		0.056	0.056			

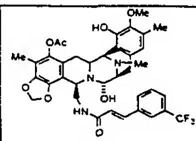
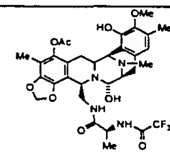
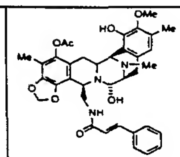
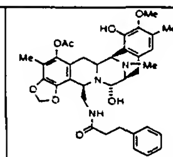
CYTOTOXIC ACTIVITY (M)

SOLID TUMORS	LINE	 **66**	 **67**	 **70**	 **80**
Bladder	5637	6.02E-10	3.42E-10	1.91E-10	2.04E-11
Breast	MX-1	1.65E-06	NA	2.38E-09	NA
Colon	HT-29	7.84E-10	1.97E-08	2.12E-09	8.44E-12
Gastric	Hs746t	7.90E-12	2.18E-09	7.10E-11	2.21E-09
Liver	SK-HEP-1	1.79E-12	6.01E-11	3.15E-09	9.91E-11
NSCL	A549	3.25E-09	7.68E-06	NA	NA
Ovary	SK-OV-3	4.39E-11	1.02E-07	8.74E-09	NA
Pancreas	PANC-1	7.22E-11	4.17E-09	1.29E-10	1.19E-10

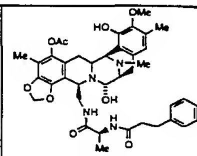
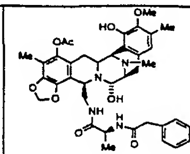
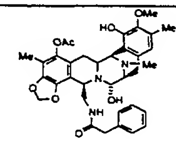
Pharnynx	FADU	5.41E-11	1.58E-09	3.71E-10	5.98E-09
Prostate	PC3	6.65E-09	2.15E-09	4.70E-09	1.52E-10
Prostate	DU-145	5.73E-10	1.83E-07	2.22E-09	NA
Prostate	LNCAP	5.45E-10	2.17E-10	3.94E-11	
Renal	786-O	6.58E-12	1.59E-09	1.72E-09	1.03E-10
SCL	NCI-H187	7.14E-14	9.57E-10	7.78E-14	
Retinoblastoma	Y-79	7.14E-14	7.36E-10	8.85E-11	
Melanoma	Mel-28	2.60E-10	3.17E-09	2.18E-09	1.23E-10
Fibrosarcoma	SW-694	9.91E-10	NA	1.39E-06	NA
Chondrosarcoma	CHSA	3.24E-10	6.77E-09	1.39E-09	2.30E-10
Osteosarcoma	OSA-FH	1.94E-09	1.39E-09	1.09E-09	1.11E-10

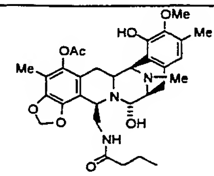
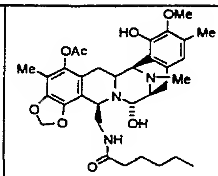
SOLID TUMORS	**LINE**	 **92**	 94	 **81**
Bladder	5637	1.65E-10	7.85E-10	3.18-09
Breast	MX-1	NA	2.85E-06	NA
Colon	HT-29	7.43E-10	1.2E-10	NA
Gastric	Hs746t	9.35E-10	6.25E-09	1.37E-07
Liver	SK-HEP-1	1.40E-09	9.03E-10	9.50E-09
NSCL	A549	NA	NA	NA
Ovary	SK-OV-3	NA	NA	
Pancreas	PANC-1	8.93E-10	2.58E-9	1.03E-08
Pharnynx	FADU	8.41E-10	3.77E-08	1.14E-09
Prostate	PC3	8.13E-10		9.34E-09
Prostate	DU-145	NA	NA	NA
Prostate	LNCAP		NA	
Renal	786-O	7.88E-10	2.90E-09	1.00E-08
SCL	NCI-H187		2.07E-12	
Retinoblastoma	Y-79		1.31E-11	7.78E-09

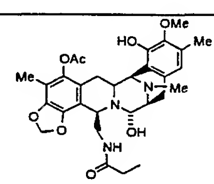
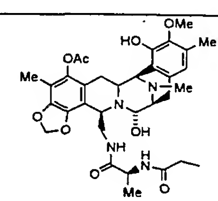
Melanoma	Mel-28	1.08E-09	1.13E-09	4.48E-09
Fibrosarcoma	SW-694	NA		
Chondrosarcoma	CHSA	1.08E-09	2.25E-09	1.09E-08
Osteosarcoma	OSA-FH	8.84E-10	1.35-08	9.50E-09

LEUKEMIAS & LYMPHOMAS	**LINE**	 **66**	 **67**	 **70**	 **80**
ALL Promyelocytic leukemia	HL60				9.38E-09
ALL Acute lymphoblastic	Molt 3	6.13E-10	2.8E-09	5.66E-10	1.55E-14
CML Chronic myelogenous	K562				2.33E-07
Leukemia Hairy B-cell	Mo-B				
Lymphoma T-cell	H9				1.99E-11
Lymphoma Cutaneus T cell	Hut 78	5.50E-11	2.57E-10	4.62E-9	6.21E-11
Lymphoma undifferentiated	MC116	2.15E-10	2.65E-10	3.8E-09	NA
Lymphoma Burkitts B celll	RAMOS				7.77E-13
Lymphoma	U-937	1.77E-10	5.27E-11	3.28E-11	3.06E-11

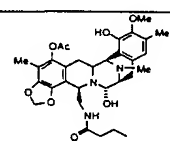
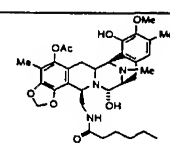
Histiocytic					

LEUKEMIAS & LYMPHOMAS	**LINE**	 **92**	 94	 **81**
ALL Promyelocytic leukemia	HL60	5.92E-09	1.23E-10	3.97E-10
ALL Acute lymphoblastic	Molt 3	7.53E-12	8.85E-10	2.54E-09
CML Chronic myelogenous	K562	1.09E-08	4.45E-08	
Leukemia Hairy B-cell	Mo-B			
Lymphoma T-cell	H9	4.48E-09	1.14E-08	
Lymphoma Cutaneus T cell	Hut 78	9.9E-10	1.06E-08	7.46E-09
Lymphoma undifferentiated	MC116	NA	1.41E-09	1.13E-08
Lymphoma Burkitts B celll	RAMOS	5.26-11	8.85E-10	7.15E-09
Lymphoma Histiocytic	U-937	5.15E-10		

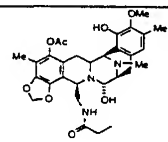
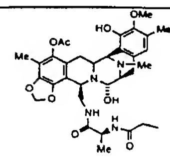
SOLID TUMORS	LINE	 71	 **93**
Bladder	5637	2.81E-09	2.84E-10
Breast	MX-1	2.50E-06	NA
Colon	HT-29	NA	8.97E-09
Gastric	Hs746t	2.97E-08	9.19E-09
Liver	SK-HEP-1	5.07E-09	1.08E-09
NSCL	A549	NA	9.41E-09
Ovary	SK-OV-3	2.21E-07	NA
Pancreas	PANC-1	2.90E-09	1.00E-09
Pharnynx	FADU	7.94E-09	1.39E-08
Prostate	PC3	1.46-08	9.32E-10
Prostate	DU-145	NA	NA
Prostate	LNCAP	5.39E-09	
Renal	786-O	6.55E-09	1.72E-09
SCL	NCI-H187	3.98E-11	
Retinoblastoma	Y-79	3.14E-09	
Melanoma	Mel-28	3.05E-08	1.15E-09
Fibrosarcoma	SW-694	NA	NA
Chondrosarcoma	CHSA	1.73E-08	2.10E-09
Osteosarcoma	OSA-FH	8.56E-08	1.30E-09

SOLID TUMORS	LINE	 82	 95
Bladder	5637	9.91E-10	1.17E-09
Breast	MX-1	NA	1.92E-09

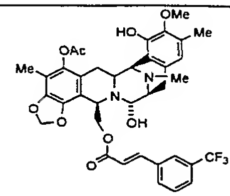
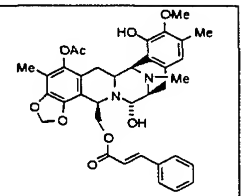
Colon	HT-29	NA	NA
Gastric	Hs746t	1.36E-09	8.15E-09
Liver	SK-HEP-1	1.17E-09	6.21E-09
NSCL	A549	NA	NA
Ovary	SK-OV-3	2.90E-08	NA
Pancreas	PANC-1	1.37E-09	8.61E-09
Pharnynx	FADU	3.05E-08	4.38E-08
Prostate	PC3		
Prostate	DU-145	NA	NA
Prostate	LNCAP	2.38E-08	1.77E-08
Renal	786-O	2.27E-09	1.54E-08
SCL	NCI-H187	2.41E-11	9.89E-11
Retinoblastoma	Y-79	3.08E-10	7.45E-10
Melanoma	Mel-28	2.85E-09	1.42E-08
Fibrosarcoma	SW-694		
Chondrosarcoma	CHSA	1.63E-09	2.91E-08
Osteosarcoma	OSA-FH	4.37E-09	1.15E-08

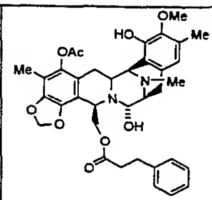
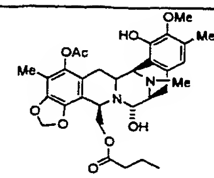
LEUKEMIAS & LYMPHOMAS	**LINE**	 71	 **93**
ALL Promyelocytic leukemia	HL60		1.50E-08
ALL Acute lymphoblastic	Molt 3	1.62E-09	3.87E-09
CML Chronic	K562		6.89E-08

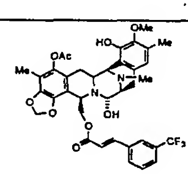
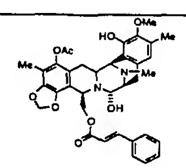
myelogenous			
Lymphoma T-cell	H9		1.08E-08
Lymphoma Cutaneus T cell	Hut 78	7.33E-09	1.97E-09
Lymphoma undifferentiated	MC116	1.62E-08	3.81E-09
Lymphoma Burkitts B celll	RAMOS		1.1E-09
Lymphoma Histiocytic	U-937	1.92E-09	1.08E-09

LEUKEMIAS & LYMPHOMAS	**LINE**	 82	 95
ALL Promyelocytic leukemia	HL60	4.93E-10	7.36E-09
ALL Acute lymphoblastic	Molt 3	9.86E-10	9.86E-10
CML Chronic myelogenous	K562	1.87E-08	1.18E-08
Lymphoma T-cell	H9	1.20E-08	2.43-08
Lymphoma Cutaneus T cell	Hut 78		
Lymphoma undifferentiated	MC116	1.04E-09	1.49E-09
Lymphoma Burkitts B celll	RAMOS		5.01E-09

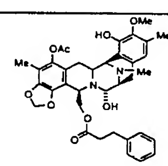
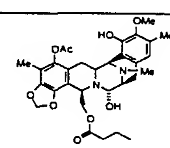
Lymphoma Histiocytic	U-937		

SOLID TUMORS	LINE	 114	 **116**
Bladder	5637	1.14E-08	1.71E-08
Breast	MX-1	2.81E-08	7.25E-13
Colon	HT-29	4.08E-07	2.96E-07
Gastric	Hs746t	3.57E-08	1.24E-09
Liver	SK-HEP-1	1.63-08	1.94E-09
NSCL	A549	2.81E-06	1.56-05
Ovary	SK-OV-3	7.03E-06	7.78E-08
Pancreas	PANC-1	1.03E-08	9.47E-09
Pharnynx	FADU	4.59E-07	2.46E-08
Prostate	PC3	7.88E-08	
Prostate	DU-145	7.03E-08	1.56E-06
Prostate	LNCAP	5.98E-07	6.83E-08
Renal	786-O	1.46E-08	5.26E-12
SCL	NCI-H187	8.02E-10	7.78E-14
Retinoblastoma	Y-79	8.85E-10	7.78E-14
Melanoma	Mel-28	1.76E-08	5.89E-08
Fibrosarcoma	SW-694	3.38E-06	6.69E-06
Chondrosarcoma	CHSA	2.53E-08	4.49E-08
Osteosarcoma	OSA-FH	6.34E-08	5.26E-07

SOLID TUMORS	**LINE**	 **115**	 **113**
Bladder	5637	7.88E-10	3.02E-08
Breast	MX-1	NA	4.75E-08
Colon	HT-29	8.99E-09	1.34E-08
Gastric	Hs746t	2.95E-08	7.05E-07
Liver	SK-HEP-1	1.29E-09	6.12E-08
NSCL	A549	8.22E-06	8.49E-09
Ovary	SK-OV-3		3.55E-08
Pancreas	PANC-1	5.68E-10	1.28E-08
Pharnynx	FADU	5.40E-11	2.47E-08
Prostate	PC3	7.71E-10	6.18E-10
Prostate	DU-145	NA	1.17E-08
Prostate	LNCAP		3.29E-07
Renal	786-O	9.23E-10	1.13E-08
SCL	NCI-H187		2.33E-10
Retinoblastoma	Y-79	1.03E-08	2.64E-09
Melanoma	Mel-28	2.23E-08	1.25E-08
Fibrosarcoma	SW-694	8.53E-06	NA
Chondrosarcoma	CHSA	1.55E-05	2.95E-08
Osteosarcoma	OSA-FH	1.29E-09	5.01E-08

LEUKEMIAS & LYMPHOMAS	**LINE**	 114	 **116**

ALL Promyelocytic leukemia	HL60		1.34E-08
ALL Acute lymphoblastic	Molt 3	1.44E-08	2.48E-09
CML Chronic myelogenous	K562	1.56E-07	6.13E-08
Lymphoma T-cell	H9	1.56E-07	1.91E-08
Lymphoma Cutaneus T cell	Hut 78	6.47E-08	7.31E-09
Lymphoma undifferentiated	MC116	1.69E-08	6.38E-09
Lymphoma Burkitts B celll	RAMOS	8.86E-09	7.15E-10
Lymphoma Histiocytic	U-937	7.6E-08	

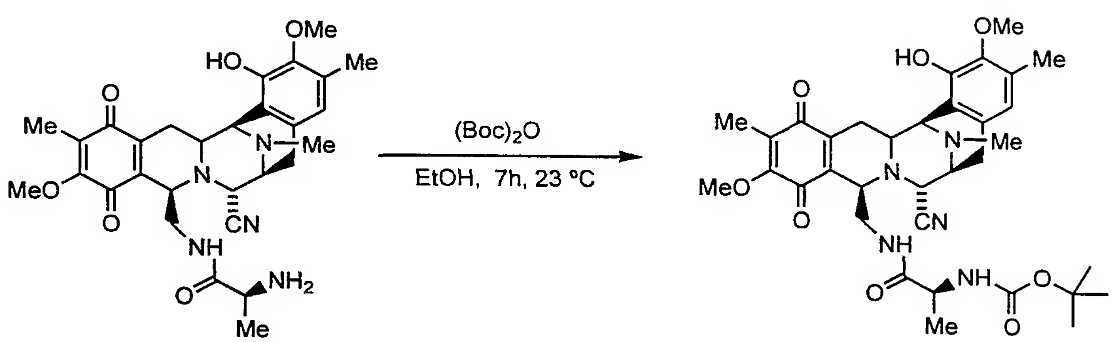
LEUKEMIAS & LYMPHOMAS	**LINE**	 **115**	 113
ALL Promyelocytic leukemia	HL60	3.1E-09	
ALL Acute lymphoblastic	Molt 3	8.69E-11	4.63E-08

CML Chronic myelogenous	K562		2.11E-08
Lymphoma T-cell	H9	2.17E-08	6.76E-08
Lymphoma Cutaneus T cell	Hut 78	4.81E-08	2.06E-08
Lymphoma undifferentiated	MC116	5.27E-11	1.51E-08
Lymphoma Burkitts B celll	RAMOS	1.86E-09	9.09E-09
Lymphoma Histiocytic	U-937		1.03E-08

EXAMPLES OF THE INVENTION

The present invention is illustrated by the following examples.

Example 1



2 14

To a solution of **2** (21.53 g, 39.17 ml) in ethanol (200 ml), *tert*-

butoxycarbonyl anhydride (7.7 g, 35.25 ml) was added and the mixture was stirred for 7 h at 23 °C. Then, the reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 6:4) to give **14** (20.6 g, 81 %) as a yellow solid.

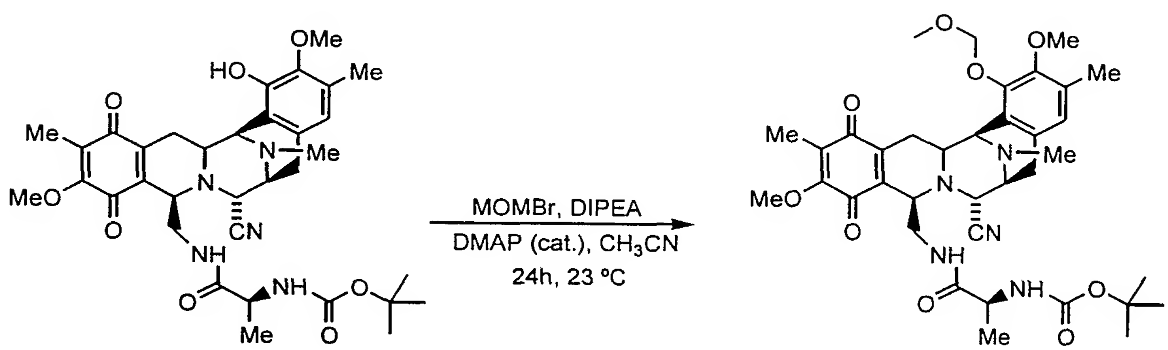
Rf: 0.52 (ethyl acetate:$CHCl_3$ 5:2).

^1H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6. 32 (bs, 1H), 5.26 (bs, 1H), 4.60 (bs, 1H), 4.14 (d, J= 2.4 Hz, 1H), 4.05 (d, J= 2.4 Hz, 1H), 3.94 (s, 3H), 3.81 (d, J= 4.8 Hz, 1H), 3.7 (s, 3H), 3.34 (br d, J= 7.2 Hz, 1H), 3.18-3.00 (m, 5H), 2.44 (d, J= 18.3 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.82 (s, 3H), 1.80-1.65 (m, 1H), 1.48 (s, 9H), 0.86 (d, J= 5.7 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.5, 180.8, 172.7, 155.9, 154.5, 147.3, 143.3, 141.5, 135.3, 130.4, 129.2, 127.5, 120.2, 117.4, 116.9, 80.2, 60.7, 60.3, 58.5, 55.9, 55.8, 54.9, 54.4, 50.0, 41.6, 40.3, 28.0, 25.3, 24.0, 18.1, 15.6, 8.5.

ESI-MS m/z: Calcd. for $C_{34}H_{43}N_5O_8$: 649.7. Found $(M+H)^+$: 650.3.

Example 2



14 15

To a stirred solution of **14** (20.6 g, 31.75 ml) in CH_3CN (159 ml), diisopropylethylamine (82.96 ml, 476.2 ml), methoxymethylene bromide (25.9 ml, 317.5 ml) and dimethylaminopyridine (155 mg, 1.27 ml) were added at 0 °C. The mixture was stirred at 23 °C for 24h. The reaction was quenched at 0 °C with aqueous 0.1N HCl (750 ml) (pH = 5), and extracted with CH_2Cl_2 (2 x 400 ml). The organic phase was dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by flash column chromatography

(SiO_2, gradient hexane:ethyl acetate 4:1 to hexane:ethyl acetate 3:2) to give **15** (17.6 g, 83 %) as a yellow solid.

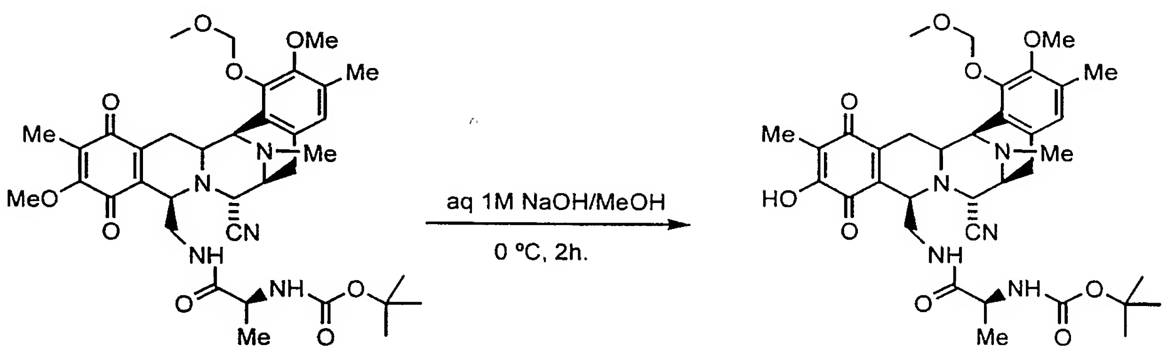
Rf: 0.38 (hexane:ethyl acetate 3:7).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 5.35 (bs, 1H), 5.13 (s, 2H), 4.50 (bs, 1H), 4.25 (d, *J*= 2.7 Hz, 1H), 4.03 (d, *J*= 2.7 Hz, 1H), 3.97 (s, 3H), 3.84 (bs, 1H), 3.82-3.65 (m, 1H), 3.69 (s, 3H), 3.56 (s, 3H), 3.39-3.37 (m, 1H), 3.20-3.00 (m, 5H), 2.46 (d, *J*= 18 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 1.85 (s, 3H), 1.73-1.63 (m, 1H), 1.29 (s, 9H), 0.93 (d, *J*= 5.1 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.4, 180.9, 172.4, 155.9, 154.5, 149.0, 148.4, 141.6, 135.1, 131.0, 129.9, 127.6, 124.4, 123.7, 117.3, 99.1, 79.3, 60.7, 59.7, 58.4, 57.5, 56.2, 55.9, 55.0, 54.2, 50.0, 41.5, 39.9, 28.0, 25.2, 24.0, 18.1, 15.6, 8.5.

ESI-MS m/z: Calcd. for $C_{36}H_{47}N_5O_9$: 693.8. Found $(M+H)^+$: 694.3.

Example 3



15

16

To a flask containing **15** (8 g, 1.5 ml) in methanol (1.6 l) an aqueous solution of 1M sodium hydroxide (3.2 l) was added at 0 °C. The reaction was stirred for 2h at this temperature and then, quenched with 6M HCl to pH = 5. The mixture was extracted with ethyl acetate (3 x 1 l) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient $CHCl_3$ to $CHCl_3$:ethyl acetate 2:1) to afford **16** (5.3 mg, 68 %).

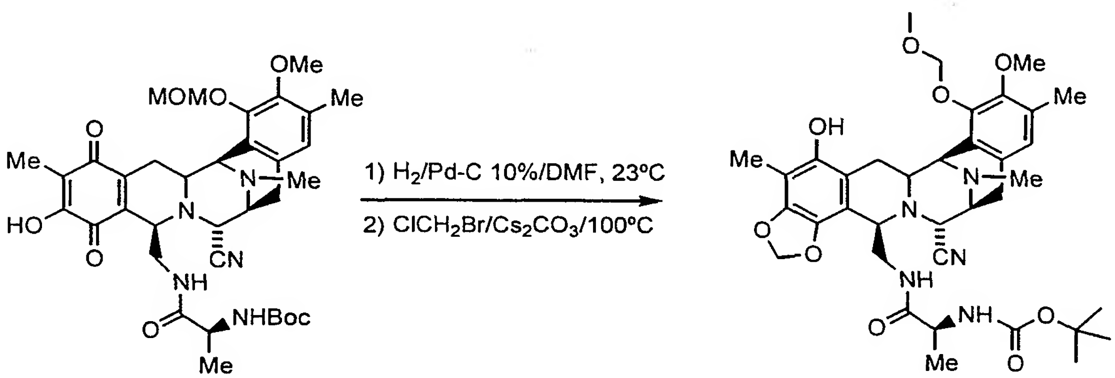
Rf: 0.48 (CH_3CN:H_2O 7:3, RP-C18)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 5.43 (bs, 1H), 5.16 (s, 2H), 4.54 (bs, 1H), 4.26 (d, J= 1.8 Hz, 1H), 4.04 (d, J= 2.7 Hz 1H), 3.84 (bs, 1H), 3.80-3.64 (m, 1H), 3.58 (s, 3H), 3.41-3.39 (m, 1H), 3.22-3.06 (m, 5H), 2.49 (d, J= 18.6 Hz 1H), 2.35 (s, 3H), 2.30-2.25 (m, 1H), 2.24 (s, 3H), 1.87 (s, 3H), 1.45-1.33 (m, 1H), 1.19 (s, 9H), 1.00 (br d, J= 6.6 Hz 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 184.9, 180.9, 172.6, 154.7, 151.3, 149.1, 148.6, 144.7, 132.9, 131.3, 129.8, 124.5, 123.7, 117.3, 116.8, 99.1, 79.4, 59.8, 58.6, 57.7, 56.2, 55.6, 54.9, 54.5, 50.1, 41.6, 40.1, 28.0, 25.3, 24.4, 18.1, 15.7, 8.0.

ESI-MS m/z: Calcd. for $C_{35}H_{45}N_5O_9$: 679.7. Found $(M+H)^+$: 680.3.

Example 4



16 17

To a degassed solution of compound **16** (1.8 g, 2.64 ml) in DMF (221 ml) 10 % Pd/C (360 mg) was added and stirred under H_2 (atmospheric pressure) for 45 min. The reaction was filtered through celite under argon, to a flask containing anhydrous Cs_2CO_3 (2.58 g, 7.92 ml). Then, bromochloromethane (3.40 ml 52.8 ml), was added and the tube was sealed and stirred at 100 °C for 2h. The reaction was cooled, filtered through a pad of celite and washed with CH_2Cl_2. The organic layer was concentrated and dried (sodium sulphate) to afford **17** as a brown oil that was used in the next step with no further purification.

Rf: 0.36 (hexane:ethyl acetate 1:5, SiO_2).

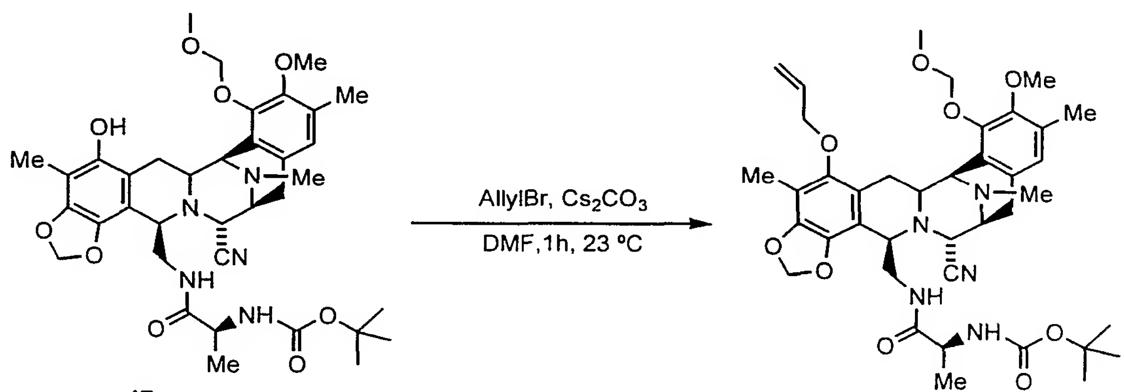
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.05 (bs, 1H), 5.90 (s, 1H), 5.79 (s, 1H), 5.40 (bs, 1H), 5.31-5.24 (m, 2H), 4.67 (d, J= 8.1 Hz, 1H), 4.19 (d, J= 2.7 Hz, 1H), 4.07 (bs, 1H), 4.01 (bs, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.64-2.96 (m, 5H), 2.65 (d, J=18.3 Hz, 1H), 2.33 (s,

3H), 2.21 (s, 3H), 2.04 (s, 3H), 2.01-1.95 (m, 1H), 1.28 (s, 9H), 0.87 (d, J= 6.3 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 162.6, 154.9, 149.1, 145.7, 135.9, 130.8, 130.7, 125.1, 123.1, 117.8, 100.8, 99.8, 76.6, 59.8, 59.2, 57.7, 57.0, 56.7, 55.8, 55.2, 49.5, 41.6, 40.1, 36.5, 31.9, 31.6, 29.7, 28.2, 26.3, 25.0, 22.6, 18.2, 15.8, 14.1, 8.8.

ESI-MS m/z: Calcd. for $C_{36}H_{47}N_5O_9$: 693.34. Found $(M+H)^+$: 694.3.

Example 5



17 18

To a flask containing a solution of **17** (1.83 g, 2.65 ml) in DMF (13 ml), Cs_2CO_3 (2.6 g, 7.97 ml), and allyl bromide (1.15 ml, 13.28 ml) were added at 0° C. The resulting mixture was stirred at 23 °C for 1h. The reaction was filtered through a pad of celite and washed with CH_2Cl_2. The organic layer was dried and concentrated (sodium sulphate). The residue was purified by flash column chromatography (SiO_2, $CHCl_3$:ethyl acetate 1:4) to afford **18** (1.08 mg, 56 %) as a white solid.

Rf: 0.36 ($CHCl_3$:ethyl acetate 1:3).

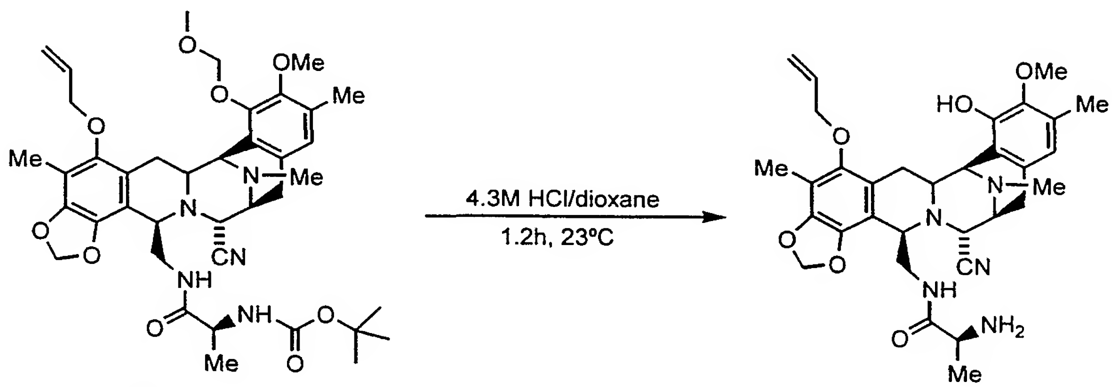
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 6.27-6.02 (m, 1H), 5.94 (s, 1H), 5.83 (s, 1H), 5.37 (dd, J_1= 1.01 Hz, J_2= 16.8 Hz, 1H), 5.40 (bs, 1H), 5.25 (dd, J_1= 1.0 Hz, J_2= 10.5 Hz, 1H), 5.10 (s, 2H), 4.91 (bs, 1H), 4.25-4.22 (m, 1H), 4.21 (d, J= 2.4 Hz, 1H), 4.14-4.10 (m, 1H), 4.08 (d, J=2.4 Hz, 1H), 4.00 (bs, 1H), 3.70 (s, 3H), 3.59 (s, 3H), 3.56-3.35 (m, 2H), 3.26-3.20 (m, 2H), 3.05-2.96 (dd, J_1= 8.1 Hz, J_2=18 Hz, 1H), 2.63 (d, J=18 Hz, 1H), 2.30 (s, 3H), 2.21 (s, 3H), 2.09 (s, 3H), 1.91-1.80 (m, 1H), 1.24 (s, 9H), 0.94 (d, J= 6.6 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 154.8, 148.8, 148.6, 148.4, 144.4, 138.8, 133.7, 130.9,

130.3, 125.1, 124.0, 120.9, 117.8, 117.4, 112.8, 112.6, 101.1, 99.2, 73.9, 59.7, 59.3, 57.7, 56.9, 56.8, 56.2, 55.2, 40.1, 34.6, 31.5, 28.1, 26.4, 25.1, 22.6, 18.5, 15.7, 14.0, 9.2.

ESI-MS m/z: Calcd. for $C_{39}H_{51}N_5O_9$: 733.4. Found $(M+H)^+$: 734.4.

Example 6



18 19

To a solution of **18** (0.1 g, 0.137 ml) in dioxane (2 ml), 4.2M HCl/dioxane (1.46 ml) was added and the mixture was stirred for 1.2h at 23 °C. The reaction was quenched at 0 °C with sat. Aqueous sodium bicarbonate (60 ml) and extracted with ethyl acetate (2x70 ml). The organic layers were dried (sodium sulphate) and concentrated *in vacuo* to afford **19** (267 mg, 95 %) as a white solid that was used in subsequent reactions with no further purification.

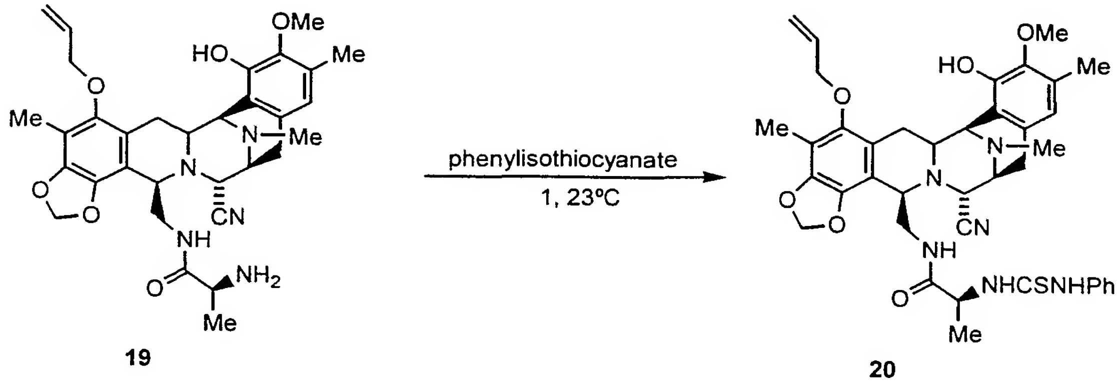
Rf: 0.17 (ethyl acetate:methanol 10:1, SiO_2)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.49 (s, 1H), 6.12-6.00 (m, 1H), 5.94 (s, 1H), 5.86 (s, 1H), 5.34 (dd, *J*= 1.0 Hz, *J*= 17.4 Hz, 1H), 5.25 (dd, *J*= 1.0 Hz, *J*= 10.2 Hz, 1H), 4.18-3.76 (m, 5H), 3.74 (s, 3H), 3.71-3.59 (m, 1H), 3.36-3.20 (m, 4H), 3.01-2.90 (m, 1H), 2.60 (d, *J*= 18.0 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.11 (s, 3H), 1.97-1.86 (m, 1H), 0.93 (d, *J*= 8.7 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 148.4, 146.7, 144.4, 142.4, 138.9, 133.7, 131.3, 128.3, 120.8, 117.9, 117.4, 113.8, 112.4, 101.1, 74.2, 60.5, 59.1, 56.5, 56.1, 56.3, 56.0, 55.0, 50.5, 41.6, 39.5, 29.5, 26.4, 24.9, 21.1, 15.5, 9.33.

ESI-MS m/z: Calcd. for $C_{32}H_{39}N_5O_6$: 589. Found $(M+H)^+$: 590.

Example 7



To a solution of **19** (250 mg, 0.42 ml) in CH_2Cl_2 (1.5 ml), phenyl isothiocyanate (0.3 ml, 2.51 ml) was added and the mixture was stirred at 23° C for 1h. The reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient Hexane to 5:1 hexane:ethyl acetate) to afford **20** (270 mg, 87 %) as a white solid.

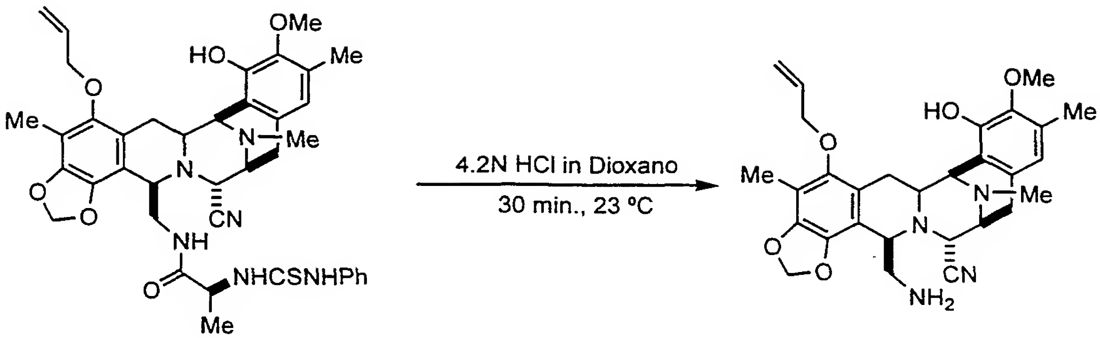
Rf: 0.56 ($CHCl_3$:ethyl acetate 1:4).

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.00 (bs, 1H), 7.45-6.97 (m, 4H), 6.10 (s, 1H), 6.08-6.00 (m, 1H), 5.92 (s, 1H), 5.89 (s, 1H), 5.82 (s, 1H), 5.40 (dd, *J*= 1.5 Hz, *J*= 17.1 Hz, 1H), 3.38 (bs, 1H), 5.23 (dd, *J*= 1.5 Hz, *J*= 10.5 Hz, 1H), 4.42-4.36 (m, 1H), 4.19-4.03 (m, 5H), 3.71 (s, 3H), 3.68-3.17 (m, 4H), 2.90 (dd, *J*=7.8 Hz, *J*= 18.3 Hz, 1H), 2.57 (d, *J*= 18.3 Hz, 1H), 2.25 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 1.90 (dd, *J*= 12.3 Hz, *J*= 16.5 Hz, 1H), 0.81 (d, *J*= 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 178.4, 171.6, 148.6, 146.8, 144.3, 142.7, 138.7, 136.2, 133.6, 130.7, 129.8, 126.6, 124.2, 124.1, 120.9, 120.5, 117.7, 117.4, 116.7, 112.6, 112.5, 101.0, 74.0, 60.6, 59.0, 57.0, 56.2, 56.1, 55.0, 53.3, 41.4, 39.7, 26.3, 24.8, 18.3, 15.5, 9.2.

ESI-MS m/z: Calcd. for $C_{39}H_{44}N_6O_6S$: 724.8 Found $(M+H)^+$: 725.3.

Example 8



20

21

To a solution of **20** (270 mg, 0.37 ml) in dioxane (1 ml), 4.2N HCl/dioxane (3.5 ml) was added and the reaction was stirred at 23 °C for 30 min. Then, ethyl acetate (20 ml) and H_2O (20 ml) were added and the organic layer was decanted. The aqueous phase was basified with saturated aqueous sodium bicarbonate (60 ml) (pH = 8) at 0 °C and then, extracted with CH_2Cl_2 (2 x 50 ml). The combined organic extracts were dried (sodium sulphate), and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ethyl acetate:methanol 5:1) to afford compound **21** (158 mg, 82%) as a white solid.

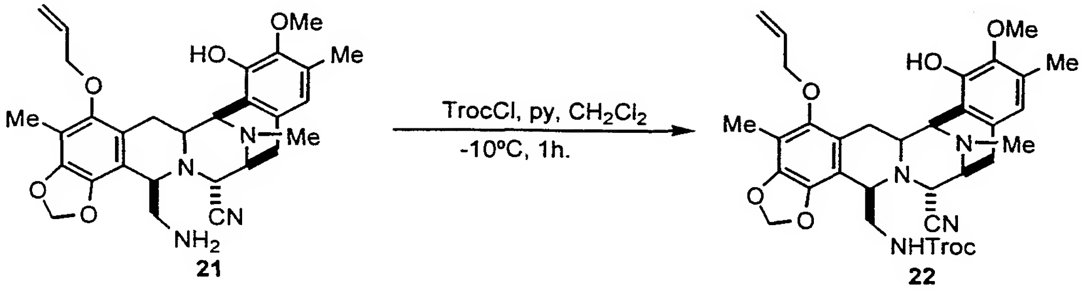
Rf: 0.3 (ethyl acetate:methanol 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 6.12-6.03 (m, 1H), 5.91 (s, 1H), 5.85 (s, 1H), 5.38 (dd, J_1= 1.2 Hz, J_2= 17.1 Hz, 1H), 5.24 (dd, J_1= 1.2 Hz, J_2= 10.5 Hz, 1H), 4.23-4.09 (m, 4H), 3.98 (d, J= 2.1 Hz, 1H), 3.90 (bs, 1H), 3.72 (s, 3H), 3.36-3.02 (m, 5H), 2.72-2.71 (m, 2H), 2.48 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 2.11 (s, 3H), 1.85 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H)).

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4, 146.7, 144.4, 142.8, 138.8, 133.8, 130.5, 128.8, 121.5, 120.8, 118.0, 117.5, 116.9, 113.6, 112.2, 101.1, 74.3, 60.7, 59.9, 58.8, 56.6, 56.5, 55.3, 44.2, 41.8, 29.7, 26.5, 25.7, 15.7, 9.4.

ESI-MS m/z: Calcd. for $C_{29}H_{34}N_4O_5$: 518.3. Found $(M+H)^+$: 519.2.

Example 9



To a solution of **21** (0.64 g, 1.22 ml) in CH_2Cl_2 (6.13 ml), pyridine (0.104 ml, 1.28 ml) and 2,2,2-trichloroethyl chloroformate (0.177 ml, 1.28 ml) were added at -10 °C. The mixture was stirred at this temperature for 1h and then, the reaction was quenched by addition of 0.1N HCl (10 ml) and extracted with CH_2Cl_2 (2 x 10 ml). The organic layer was dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, (hexane:ethyl acetate 1:2) to afford **22** (0.84 g, 98%) as a white foam solid.

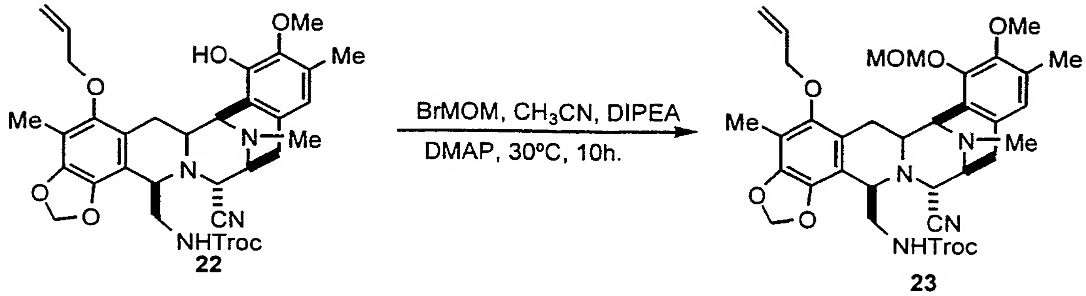
Rf: 0.57 (ethyl acetate:methanol 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 6.10-6.00 (m, 1H), 6.94 (d, J= 1.5 Hz, 1H), 5.87 (d, J= 1.5 Hz, 1H), 5.73 (bs, 1H), 5.37 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.26 (dq, J_1= 1.8 Hz, J_2= 10.2 Hz, 1H), 4.60 (d, J= 12 Hz, 1H), 4.22-4.10 (m, 4H), 4.19 (d, J= 12 Hz, 1H), 4.02 (m, 2H), 3.75 (s, 3H), 3.37-3.18 (m, 5H), 3.04 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.63 (d, J= 18 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 1.85 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 148.5, 146.7, 144.5, 142.8, 139.0, 133.8, 130.7, 128.7, 121.3, 120.8, 117.8, 117.7, 116.8, 112.7, 101.2, 77.2, 74.3, 60.7, 59.9, 57.0, 56.4, 55.3, 43.3, 41.7, 31.6, 26.4, 25.3, 22.6, 15.9, 14.1, 9.4.

ESI-MS m/z: Calcd. for $C_{32}H_{35}Cl_3N_4O_7$: 694.17. Found $(M+H)^+$: 695.2.

Example 10



To a solution of **22** (0.32 g, 0.46 ml) in CH_3CN (2.33 ml). diisopropylethylamine (1.62 ml, 9.34 ml), bromomethyl methyl ether (0.57 ml, 7.0 ml) and dimethylaminopyridine (6 mg, 0.046 ml) were added at 0 °C. The mixture was heated at 30 °C for 10h. Then, the reaction was diluted with dichloromethane (30 ml) and poured in an aqueous solution of HCl at pH = 5 (10 ml). The organic layer was dried over sodium sulphate and the solvent was eliminated under reduced pressure to give a residue which was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 2:1) to afford **23** (0.304 g, 88%) as a white foam solid.

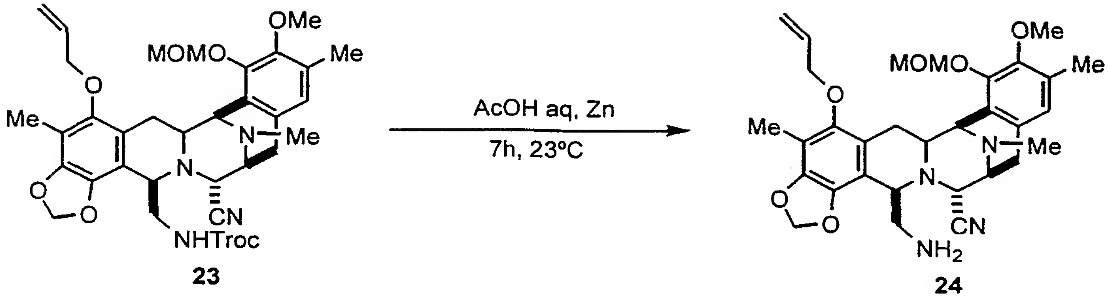
Rf: 0.62 (hexane:ethyl acetate 1:3).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (s, 1H), 6.10 (m, 1H), 5.94 (d, J= 1.5 Hz, 1H), 5.88 (d, J= 1.5 Hz, 1H), 5.39 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.26 (dq, J_1= 1.8 Hz, J_2= 10.2 Hz, 1H), 5.12 (s, 2H), 4.61 (d, J= 12 Hz, 1H), 4.55 (t, J= 6.6 Hz, 1H), 4.25 (d, J= 12 Hz, 1H), 4.22-4.11 (m, 4H), 4.03 (m, 2H), 3.72 (s, 3H), 3.58 (s, 3H), 3.38-3.21 (m, 5H), 3.05 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.65 (d, J= 18 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.12 (s, 3H), 1.79 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 148.6, 148.4, 144.5, 139.0, 133.6, 130.6, 130.1, 125.07, 124.7, 124.0, 121.1, 117.7, 112.6, 101.2, 99.2, 77.2, 74.4, 74.1, 59.8, 59.8, 57.7, 57.0, 56.8, 56.68, 55.3, 43.2, 41.5, 26.4, 25.2, 15.9, 9.3.

ESI-MS m/z: Calcd. for $C_{34}H_{39}Cl_3N_4O_8$: 738.20. Found $(M+H)^+$: 739.0.

Example 11



To a suspension of **23** (0.304 g, 0.41 ml) in 90% aqueous acetic acid (4 ml), powder zinc (0.2 g, 6.17 ml) was added and the reaction was stirred for 7 hour at 23 °C. The mixture was filtered through a pad of celite which was washed with CH_2Cl_2. The organic layer was washed with an aqueous sat. solution of sodium bicarbonate (pH = 9) (15 ml) and dried over sodium sulphate. The solvent was eliminated under reduced pressure to give **24** (0.191 g, 83%) as a white solid.

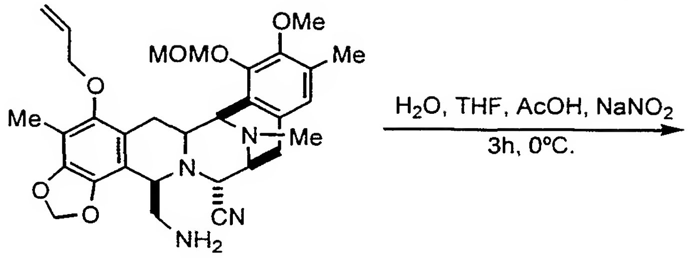
Rf: 0.3 (ethyl acetate:methanol 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.09 (m, 1H), 5.90 (d, J= 1.5 Hz, 1H), 5.83 (d, J= 1.5 Hz, 1H), 5.39 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.25 (dq, J_1= 1.5 Hz, J_2= 10.2 Hz, 1H), 5.10 (s, 2H), 4.22-4.09 (m, 3H), 3.98 (d, J= 2.4 Hz, 1H), 3.89 (m, 1H), 3.69 (s, 3H), 3.57 (s, 3H), 3.37-3.17 (m, 3H), 3.07 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.71 (m, 2H), 2.48 (d, J= 18 Hz, 1H), 2.33 (s, 3H), 2.19 (s, 3H), 2.17 (s, 3H), 1.80 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.2, 144.3, 138.7, 133.7, 130.7, 129.9, 125.0, 123.9, 121.3, 117.9, 117.5, 113.6, 112.0, 101.0, 99.2, 74.0, 59.8, 59.7, 58.8, 57.6, 57.0, 56.2, 55.2, 44.2, 41.5, 31.5, 26.4, 25.6, 22.5, 16.7, 14.0, 9.2.

ESI-MS m/z: Calcd. for $C_{31}H_{38}N_4O_6$: 562.66. Found $(M+H)^+$: 563.1.

Example 12



24 25

To a solution of **24** (20 mg, 0.035 ml), in H_2O (0.7 ml) and THF (0.7 ml). $NaNO_2$ (12 mg, 0.17 ml) and 90% aqueous AcOH (0.06 ml) were added at 0 °C and the mixture was stirred at 0 °C for 3h. After dilution with CH_2Cl_2 (5 ml), the organic layer was washed with water (1 ml), dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 2:1) to afford **25** (9.8 mg, 50%) as a white solid.

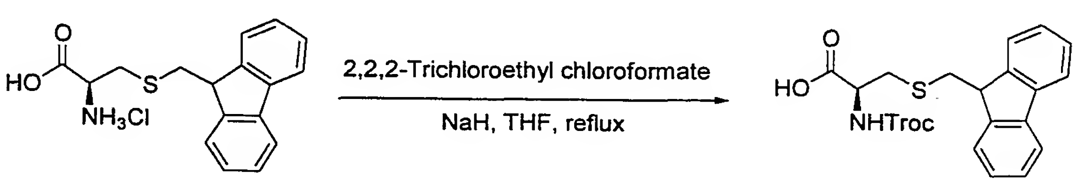
Rf: 0.34 (hexane:ethyl acetate 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 1H), 6.11 (m, 1H), 5.92 (d, J= 1.5 Hz, 1H), 5.87 (d, J= 1.5 Hz, 1H), 5.42 (dq, J_1= 1.5 Hz, J_2= 17.1 Hz, 1H), 5.28 (dq, J_1= 1.5 Hz, J_2= 10.2 Hz, 1H), 5.12 (s, 2H), 4.26-4.09 (m, 3H), 4.05 (d, J= 2.4 Hz, 1H), 3.97 (t, J= 3.0 Hz, 1H), 3.70 (s, 3H), 3.67-3.32 (m, 4H), 3.58 (s, 3H), 3.24 (dd, J_1= 2.7 Hz, J_2= 15.9 Hz, 1H), 3.12 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.51 (d, J= 18 Hz, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 2.12 (s, 3H), 1.83 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 148.4, 138.9, 133.7, 131.1, 129.4, 125.1, 123.9, 120.7, 117.6, 117.5, 113.2, 112.3, 101.1, 99.2, 74.0, 63.2, 59.8, 59.7, 57.9, 57.7, 57.0, 56.5, 55.2, 41.6, 29.6, 26.1, 25.6, 22.6, 15.7, 9.2.

ESI-MS m/z: Calcd. for $C_{31}H_{37}N_3O_7$: 563.64. Found $(M+H)^+$: 564.1.

Example 13



29

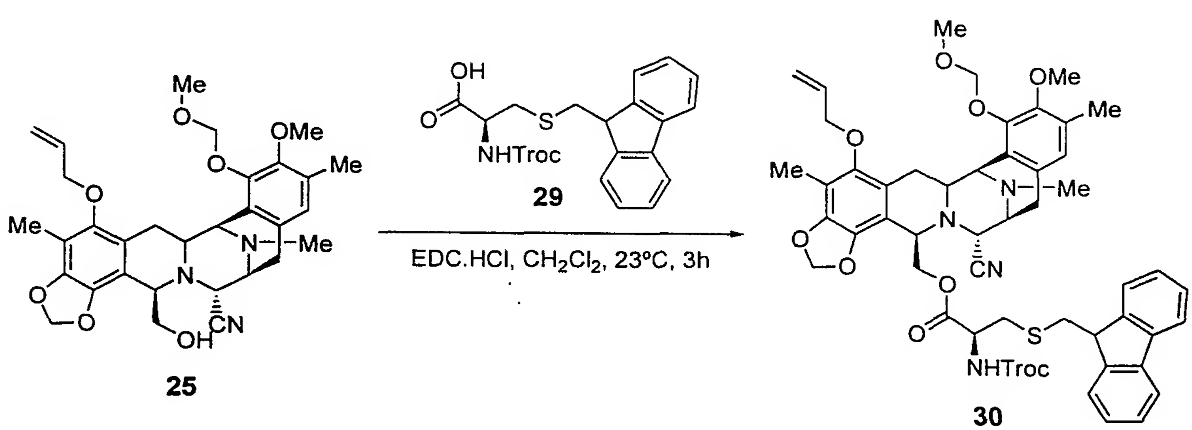
The starting material (2.0 g, 5.90 ml) was added to a suspension of sodium hydride (354 mg, 8.86 ml) in THF (40 ml) at 23 °C, following the suspension was treated with allyl chloroformate (1.135 ml, 8.25 ml) at 23 °C and then refluxed for 3 hours. The suspension was cooled, filtered off, the solid washed with ethyl acetate (100 ml), and the filtrate was concentrated. The oil crude was ground with hexane (100 ml) and kept at 4°C overnight. After, the solvent was decanted and the light yellow slurry was treated with CH_2Cl_2 (20 ml), and precipitated with hexane (100 ml). After 10 minutes, the solvent was decanted again. The operation was repeated until appearing a white solid. The white solid was filtered off and dried to afford compound **29** (1.80 g, 65%) as a white solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.74 (d, J= 7.5 Hz, 2H), 7.62 (d, J= 6.9 Hz, 2H), 7.33 (t, J= 7.5 Hz, 2H), 7.30 (t, J= 6.3 Hz, 2H), 5.71 (d, J= 7.8 Hz, 1H), 4.73 (d, J= 7.8 Hz, 2H), 4.59 (m, 1H), 4.11 (t, J= 6.0 Hz, 1H), 3.17 (dd, J= 6.0 Hz, J= 2.7 Hz, 2H), 3.20 (dd, J= 5.4 Hz, J= 2.1 Hz, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 173.6, 152.7, 144.0, 139.7, 137.8, 126.0, 125.6, 123.4, 118.3, 73.4, 52.4, 45.5, 35.8, 33.7.

ESI-MS m/z: Calcd.. for $C_{20}H_{18}Cl_3NO_4S$: 474.8. Found $(M+Na)^+$: 497.8

Example 14



A mixture of compound **25** (585 mg, 1.03 ml) and compound **29** (1.47 mg, 3.11 ml) were azeotroped with anhydrous toluene (3 x 10 ml). To a solution of **25** and **29** in anhydrous

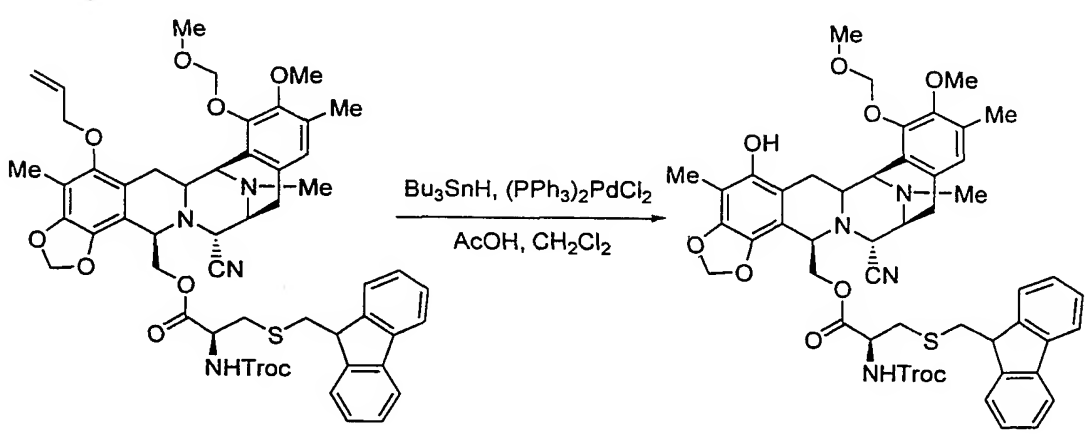
CH_2Cl_2 (40 ml) was added DMAP (633 mg, 5.18 ml) and EDC·HCl (994 mg, 5.18 ml) at 23 °C. The reaction mixture was stirred at 23 °C for 3 hours. The mixture was partitioned with saturated aqueous solution of sodium bicarbonate (50 ml) and the layers were separated. The aqueous layer was washed with CH_2Cl_2 (50 ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane 1:3) to obtain **30** (1.00 g, 95%) as a pale cream yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.52 (m, 2H), 7.38 (m, 2H), 7.28 (m, 2H), 6.65 (s, 1H), 6.03 (m, 1H), 5.92 (d, *J*= 1.5 Hz, 1H), 5.79 (d, *J*= 1.5 Hz, 1H), 5.39 (m, 1H), 5.29 (dq, *J*= 10.3 Hz, *J*= 1.5 Hz, 1H), 5.10 (s, 2H), 4.73 (d, *J*= 11.9 Hz, 1H), 4.66 (d, *J*= 11.9 Hz, 1H), 4.53 (m, 1H), 4.36-3.96 (m, 9H), 3.89 (t, *J*= 6.4 Hz, 1H), 3.71 (s, 3H), 3.55 (s, 3H), 3.33 (m, 1H), 3.20 (m, 2H), 2.94 (m, 3H), 2.59 (m, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 2.02 (s, 3H), 1.83 (dd, *J*= 16.0 Hz, *J*= 11.9 Hz, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 169.7, 154.0, 148.8, 148.4, 145.7, 144.5, 140.9, 139.0, 133.7, 130.9, 130.6, 127.6, 127.0, 124.8, 124.6, 124.1, 120.8, 119.9, 118.2, 117.7, 117.3, 112.7, 112.1, 101.3, 99.2, 74.7, 73.9, 64.4, 59.8, 57.7, 57.0, 56.8, 55.4, 53.3, 46.7, 41.4, 36.5, 34.7, 31.5, 26.4, 24.9, 22.6, 15.7, 14.0, 9.1.

ESI-MS m/z: Calcd.. for $C_{51}H_{53}Cl_3N_4O_{10}S$: 1020.4. Found $(M+H)^+$: 1021.2

Example 15



30 **31**

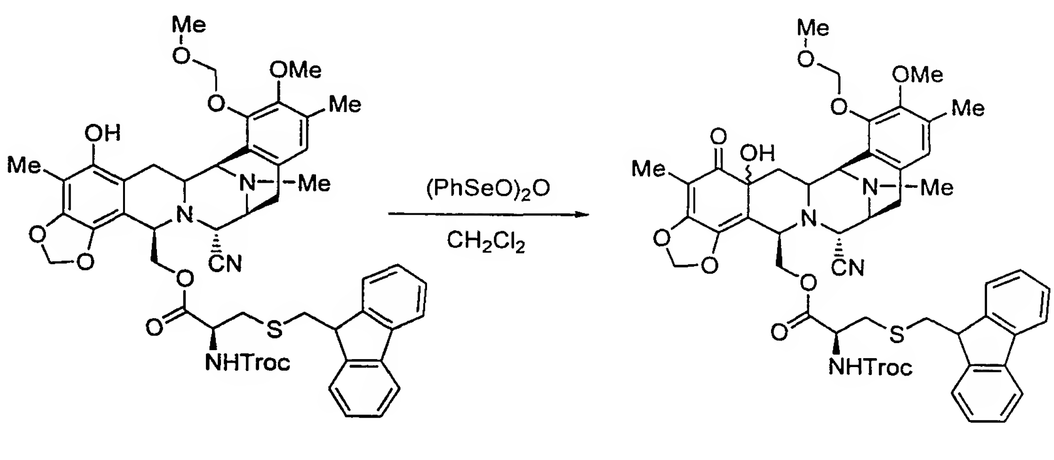
To a solution of **30** (845 mg, 0.82 ml), acetic acid (500 mg, 8.28 ml) and $(PPh_3)_2PdCl_2$ (29 mg, 0.04 ml) in anhydrous CH_2Cl_2 20 ml at 23 °C was added, dropwise, Bu_3SnH (650 mg, 2.23 ml). The reaction mixture was stirred at this temperature for 15 min., bubbling was. The crude was quenched with water (50ml) and extracted with CH_2Cl_2 (3 x 50 ml). The organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane in gradient from 1:5 to 1:3) to obtain compound **31** (730 mg, 90%) as a pale cream yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (m, 2H), 7.56 (m, 2H), 7.37 (m, 2H), 7.30 (m, 2H), 6.65 (s, 1H), 5.89 (s, 1H), 5.77 (s, 1H), 5.74 (s, 1H), 5.36 (d, *J*= 5.9 Hz, 1H), 5.32 (d, *J*= 5.9 Hz, 1H), 5.20 (d, *J*= 9.0, 1H), 4.75 (d, *J*= 12.0 Hz, 1H), 4.73 (m, 1H), 4.48 (d, *J*= 11.9 Hz, 1H), 4.08 (m, 4H), 3.89 (m, 1H), 3.86, (t, *J*= 6.2 Hz, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.38 (m, 1H), 3.25 (m, 1H), 3.02-2.89 (m, 4H), 2.67 (s, 1H), 2.61 (s, 1H), 2.51 (dd, *J*= 14.3 Hz, *J*= 4.5 Hz, 1H), 2.29 (s, 3H), 2.23 (s, 3H), 1.95 (s, 3H), 1.83 (m, 1H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.2, 152.5, 148.1, 146.2, 144.4, 144.3, 143.3, 139.6, 134.6, 129.7, 129.6, 126.2, 125.6, 123.4, 123.3, 121.6, 118.5, 116.3, 110.7, 110.2, 105.1, 99.4, 98.5, 75.2, 73.3, 61.7, 58.4, 57.9, 56.3, 56.1, 55.1, 54.7, 53.9, 51.9, 45.2, 40.1, 35.6, 33.3, 24.8, 23.3., 14.5, 7.3.

ESI-MS m/z: Calcd.. for $C_{48}H_{49}Cl_3N_4O_{10}S$: 980.3. Found $(M+H)^+$: 981.2

Example 16



31 **32**

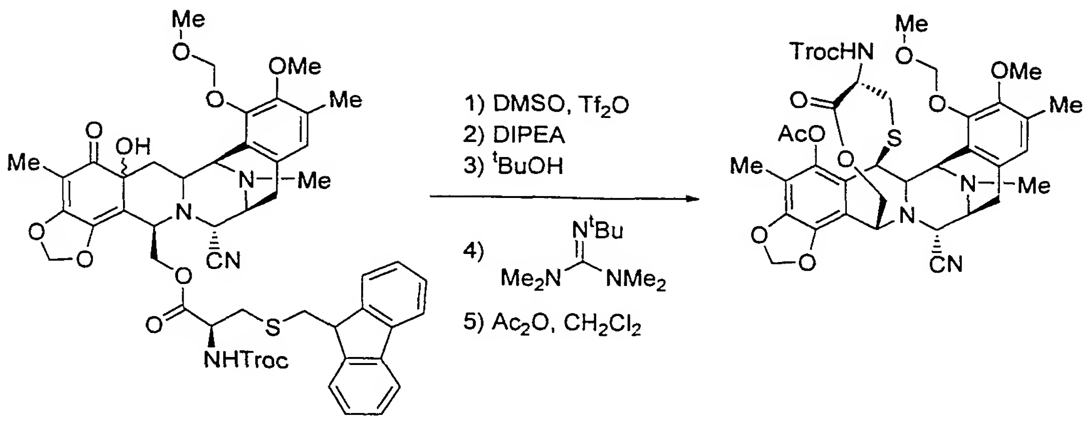
To a solution of **31** (310 mg, 0.32 ml), in anhydrous CH_2Cl_2 (15 ml) at -10 °C was added a solution of benzeneseleninic anhydride 70 % (165 mg, 0.32 ml), in anhydrous CH_2Cl_2 (7 ml), *via* cannula, keeping the temperature at -10 °C. The reaction mixture was stirred at -10 °C for 5 min. A saturated solution of sodium bicarbonate (30 ml) was added at this temperature. The aqueous layer was washed with more CH_2Cl_2 (40 ml). The organic layers were dried over sodium sulphate, filtered and concentrated. The crude was purified by flash column chromatography (ethyl acetate/hexane in gradient from 1:5 to 1:1) to obtain 32 (287 mg, 91%, HPLC: 91.3%) as a pale cream yellow solid and as a mixture of two isomers (65:35) which were used in the next step.

^{1}H-NMR (300 MHz, $CDCl_3$): δ (Mixture of isomers) 7.76 (m, 4H), 7.65 (m, 4H), 7.39 (m, 4H), 7.29 (m, 4H), 6.62 (s, 1H), 6.55 (s, 1H), 5.79-5.63 (m, 6H), 5.09 (s, 1H), 5.02 (d, *J*= 6.0 Hz, 1H), 4.99 (d, *J*= 6.0 Hz, 1H), 4.80-4.63 (m, 6H), 4.60 (m, 1H), 4.50 (m, 1H), 4.38 (d, *J*= 12.8 Hz, *J*= 7.5 Hz, 1H), 4.27 (dd, *J*= 12.8 Hz, *J*= 7.5 Hz, 1H), 4.16-3.90 (m, 10H), 3.84 (s, 3H), 3.62 (s, 3H), 3.50 (s, 3H), 3.49 (s, 3H), 3.33-2.83 (m, 14H), 2.45-2.18 (m, 2H), 2.21 (s, 6H), 2.17 (s, 6H), 1.77 (s, 6H), 1.67 (m, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ (Mixture of isomers) 168.6, 168.4, 158.6, 154.8, 152.8, 152.5, 147.3, 147.2, 146.8, 144.1, 144.0, 140.8, 139.7, 137.1, 129.8, 129.3, 128.4, 128.7, 126.5, 125.5, 123.7, 123.6, 123.5, 123.4, 122.2, 121.3, 118.3, 115.8, 115.5, 110.2, 106.9, 103.5, 103.2, 100.1, 99.6, 97.9, 97.7, 93.8, 73.4, 70.9, 69.2, 64.9, 62.5, 59.3, 58.9, 58.4, 56.7, 56.3, 56.2, 55.4, 55.2, 55.1, 54.9, 54.7, 54.3, 54.1, 53.8, 52.8, 45.5, 40.5, 40.0, 39.8, 35.8, 35.5, 33.9, 33.7, 30.1, 28.8, 24.2, 24.1, 21.2, 14.5, 14.4, 12.7, 6.0, 5.7.

ESI-MS m/z: Calcd.. for $C_{48}H_{49}Cl_3N_4O_{11}S$: 996.3. Found $(M+H)^+$: 997.2

Example 17



32 33

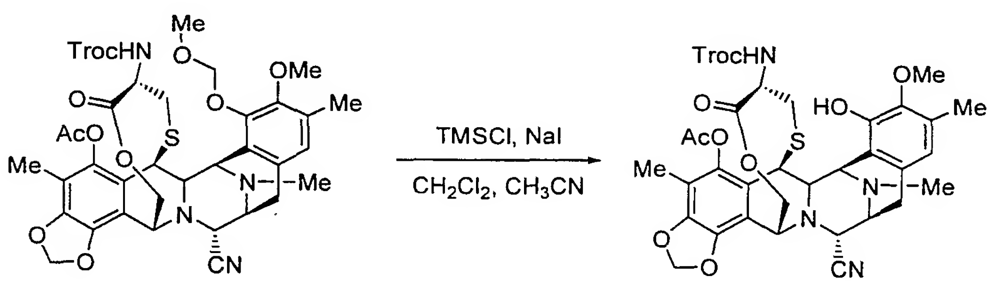
The reaction flask was flamed twice, purged vacuum/Argon several times and kept under Argon atmosphere for the reaction. To a solution of DMSO (39.1 ml, 0.55 ml, 5 equivalents.) in anhydrous CH_2Cl_2 (4.5 ml) was dropwise added triflic anhydride (37.3 ml, 0.22 ml, 2 equivalents.) at -78 °C . The reaction mixture was stirred at -78 °C for 20 minutes, then a solution of **32** (110 mg, 0.11 ml, HPLC: 91.3%) in anhydrous CH_2Cl_2 (1 ml, for the main addition and 0.5 ml for wash) at -78 °C was added, *via* cannula. During the addition the temperature was kept at -78 °C in both flasks and the colour changed from yellow to brown. The reaction mixture was stirred at -40 °C for 35 minutes. During this period of time the solution was turned from yellow to dark green. After this time, $^iPr_2NEt$ (153 ml, 0.88 ml, 8 equivalents.) was dropwise added and the reaction mixture was kept at 0 °C for 45 minutes, the colour of the solution turned to brown during this time. Then t-butanol (41.6 ml, 0.44 ml, 4 equivalents.) and 2-^{t}Butyl-1,1,3,3-tetramethylguanidine (132.8 ml, 0.77 ml, 7 equivalents.) were dropwise added and the reaction mixture was stirred at 23 °C for 40 minutes. After this time, acetic anhydride (104.3 ml, 1.10 ml, 10 equivalents.) was dropwise added and the reaction mixture was kept at 23 °C for 1 hour more. Then the reaction mixture was diluted with CH_2Cl_2 (20ml) and washed with aqueous saturated solution of NH_4Cl (50ml), sodium bicarbonate (50ml), and sodium chloride (50ml). The combined organic layers were dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography (eluent: ethyl acetate/hexane gradient from 1:3 to 1:2) to afford compound **33** (54 mg, 58%) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.09 (s, 1H), 5.99 (s, 1H), 5.20 (d, J= 5.8 Hz, 1H), 5.14 (d, J= 5.3 Hz, 1H), 5.03 (m, 1H), 4.82 (d, J= 12.2, 1H), 4.63 (d, J= 12.0 Hz, 1H), 4.52 (m, 1H), 4.35-4.17 (m, 4H), 3.76 (s, 3H), 3.56 (s, 3H), 3.45 (m, 2H), 2.91 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.12 (m, 2H), 2.03 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 168.5, 167.2, 152.7, 148.1, 147.1, 144.5, 139.6, 139.1, 130.5, 129.0, 123.7, 123.5, 123.3, 118.8, 116.5, 112.1, 100.6, 97.8, 73.3, 60.5, 59.4, 59.2, 58.3, 57.6, 57.4, 56.1, 53.3, 53.1, 40.6, 40.0, 31.0, 22.2, 18.9, 14.4, 8.1.

ESI-MS m/z: Calcd.. for $C_{36}H_{39}Cl_3N_4O_{11}S$: 842.1. Found $(M+H)^+$: 843.1

Example 18



33 **34**

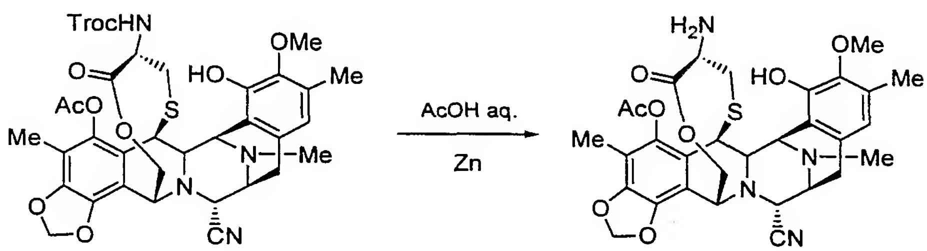
To a solution of **33** (12 mg, 0.014 ml)in dry dichloromethane (1.2 ml) and HPLC grade acetonitrile (1.2 ml) was added at 23 °C sodium iodide (21 mg, 0.14 ml) and freshly distilled (over calcium hydride at atmospheric pressure) trimethylsilyl chloride (15.4 mg, 0.14 ml). The reaction mixture turned to orange colour. After 15 min the solution was diluted with dichloromethane (10 ml) and was washed with a freshly aqueous saturated solution of $Na_2S_2O_4$ (3 x 10 ml). The organic layer was dried over sodium sulphate, filtered and concentrated. It was obtained compound **34** (13 mg, quantitative) as pale yellow solid which was used without further purification.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.85 (s, 1H), 6.09 (s, 1H), 5.99 (s, 1H), 5.27 (d, J= 5.8 Hz, 1H), 5.14 (d, J= 5.3 Hz, 1H), 5.03 (d, J= 11.9 Hz, 1H), 4.82 (d, J= 12.2, 1H), 4.63 (d, J= 13.0 Hz, 1H), 4.52 (m, 1H), 4.34 (m, 1H), 4.27 (bs, 1H), 4.18 (m, 2H), 3.76 (s, 3H), 3.56 (s, 3H), 3.44 (m, 1H), 3.42 (m, 1H), 2.91 (m, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.21 (s, 3H), 2.03

(s, 3H).

ESI-MS m/z: Calcd.. for $C_{34}H_{35}N_4O_{10}S$: 798.1. Found $(M+H)^+$: 799.1

Example 19



34 **35**

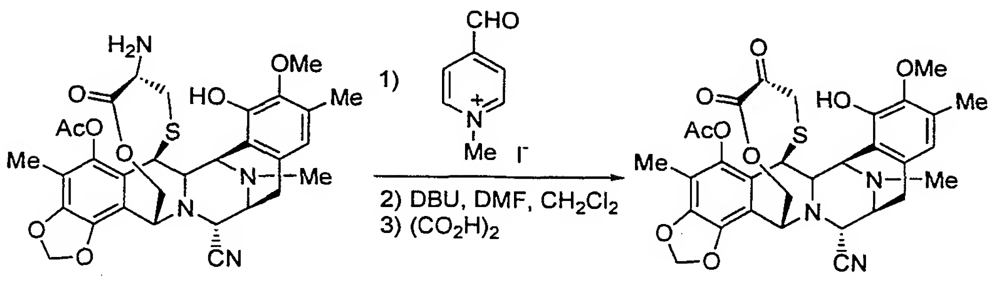
To a solution of **34** (13 mg, 0.016 ml) in a mixture of acetic acid/H_2O (90:10, 1 ml) was added powder Zinc (5.3 mg, 0.081 ml) at 23 °C. The reaction mixture was heated at 70 °C for 6 h. After this time, was cooled to 23 °C, diluted with CH_2Cl_2 (20 ml) and washed with aqueous saturated solution of sodium bicarbonate (15 ml) and aqueous solution of Et_3N (15 ml). The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography with Silica-NH_2 (eluent: ethyl acetate/hexane gradient from 0:100 to 50:50) to afford compound **35** (6.8 mg, 77% for two steps) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 6.03 (dd, J= 1.3 Hz, J= 26.5 Hz, 2H), 5.75 (bs, 1H), 5.02 (d, J= 11.6 Hz, 1H), 4.52 (m, 1H), 4.25 (m, 2H), 4.18 (d, J= 2.5 Hz, 1H), 4.12 (dd, J= 1.9 Hz, J= 11.5 Hz, 1H), 3.77 (s, 3H), 3.40 (m, 2H), 3.26 (t, J= 6.4 Hz, 1H), 2. 88 (m, 2H), 2.30-2.10 (m, 2H), 2.30 (s, 3H), 2.28 (s, 3H), 2.18 (s, 3H), 2.02 (s, 3H).

^{13}C-NMR (75 MHz, $CDCl_3$): δ 174.1, 168.4, 147.8, 145.4, 142.9, 140.8, 140.1, 131.7, 130.2, 129.1, 128.3, 120.4, 118.3, 117.9, 113.8, 111.7, 101.7, 61.2, 59.8, 59.2, 58.9, 54.4, 53.8, 54.4, 41.3, 41.5, 34.1, 23.6, 20.3, 15.5, 9.4.

ESI-MS m/z: Calcd.. for $C_{31}H_{34}N_4O_8S$: 622.7. Found $(M+H)^+$: 623.2.

Example 20



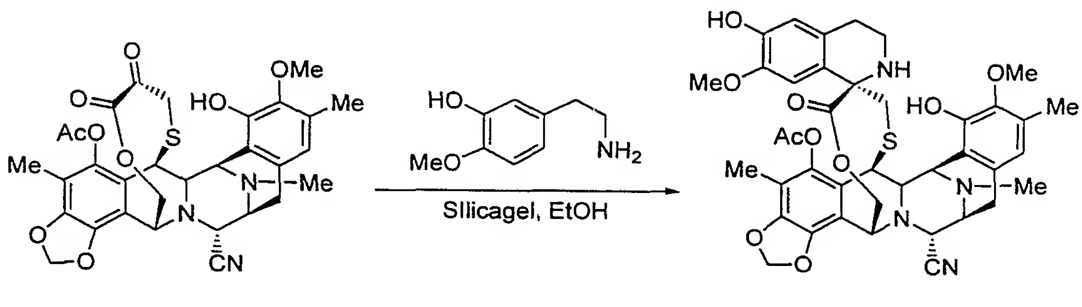
35 **36**

A solution of *N*-methyl pyridine-4-carboxaldehyde iodide (378 mg, 1.5 mmol) in anhydrous DMF (5.8 mL) was treated with anhydrous toluene (2 x 10 mL) to eliminate the amount of water by azeotropic removal of the toluene. A solution of **35** (134 mg, 0.21 mmol), previously treated with anhydrous toluene (2 x 10 mL), in anhydrous CH_2Cl_2 (distilled over CaH_2, 7.2 mL) was added, *via* cannula, at 23 °C to this orange solution. The reaction mixture was stirred at 23 °C for 4 hours. After this time DBU (32.2 µL, 0.21mmol) was dropwise added at 23 °C and it was stirred for 15 minutes at 23 °C. A freshly aqueous saturated solution of oxalic acid (5.8 mL) was added to the reaction mixture and was stirred for 30 minutes at 23 °C. Then the reaction mixture was cooled to 0 °C and $NaHCO_3$ was portionwise added followed by addittion of aqueous saturated solution of $NaHCO_3$. The mixture was extracted with Et_2O. K_2CO_3 was added to the aqueous layer and it was extrated with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (AcOEt/hexane from 1/3 to 1/1) to afford compound **36** (77 mg, 57%) as pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.48 (s, 1H), 6.11 (d, *J*= 1.3 Hz, 1H), 6.02 (d, *J*= 1.3 Hz, 1H), 5.70 (bs, 1H), 5.09 (d, *J*= 11.3 Hz, 1H), 4.66 (bs, 1H), 4.39 (m, 1H), 4.27 (d, *J*= 5.6 Hz, 1H), 4.21 (d, *J*= 10.5 Hz, 1H), 4.16 (d, *J*= 2.6 Hz, 1H), 3.76 (s, 3H), 3.54 (d, *J*= 5.1 Hz, 1H), 3.42 (d, *J*= 8.5 Hz, 1H), 2.88-2.54 (m, 3H), 2.32 (s, 3H), 2.24 (s, 3H), 2.14 (s, 3H), 2.04 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 186.7, 168.5, 160.5, 147.1, 146.4, 142.9, 141.6, 140.7, 130.4, 129.8, 121.7 (2C), 120.0, 117.8, 117.1, 113.5, 102.2, 61.7, 61.4, 60.3, 59.8, 58.9, 54.6, 41.6, 36.9, 29.7, 24.1, 20.3, 15.8, 14.1, 9.6.

ESI-MS m/z: Calcd.. for $C_{31}H_{31}N_3O_9S$: 621.7. Found $(M+H)^+$: 622.2.

Example 21



36

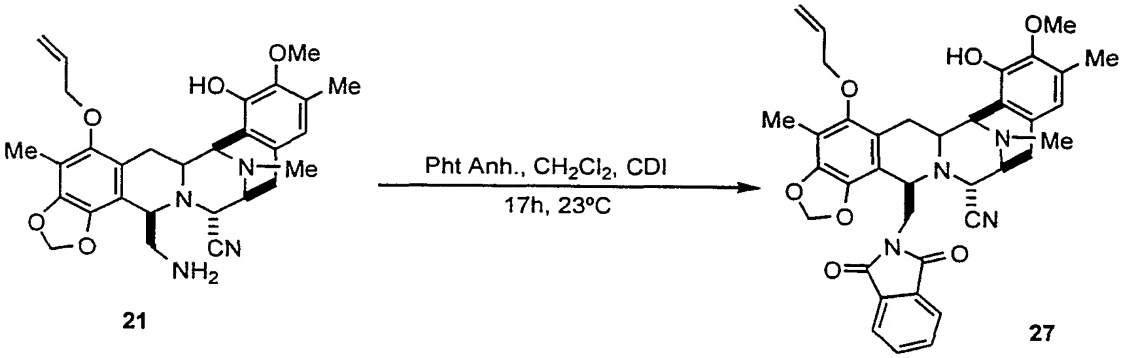
Et-770

To a solution of **36** (49mg, 0.08 ml) and 2-[3-hydroxy-4-methoxyphenyl]ethylamine (46.2 mg, 0.27 ml) in ethanol (2.5 ml) was added silica gel (105 mg) at 23 °C. The reaction mixture was stirred at 23 °C for 14 h. It was diluted with hexane and poured into a column of chromatography (ethyl acetate/hexane from 1/3 to 1/1) to afford **Et-770** (55 mg, 90%) as a pale yellow solid.

^{1}H-NMR (300 MHz, $CDCl_3$): δ 6.60 (s, 1H), 6.47 (s, 1H), 6.45 (s, 1H), 6.05 (s, 1H), 5.98 (s, 1H), 5.02 (d, *J*=11.4 Hz, 1H), 4.57 (bs, 1H), 4.32 (bs, 1H), 4.28 (d, *J*= 5.3 Hz, 1H), 4.18 (d, *J*= 2.5 Hz, 1H), 4.12 (dd, *J*= 2.1 Hz, *J*= 11.5 Hz, 1H), 3.78 (s, 3H), 3.62 (s, 3H), 3.50 (d, *J*= 5.0 Hz, 1H), 3.42 (m, 1H), 3.10 (ddd, *J*= 4.0 Hz, *J*= 10.0 Hz, *J*= 11.0 Hz, 1H), 2.94 (m, 2H), 2.79 (m, 1H), 2.61 (m, 1H), 2.47 (m, 1H), 2.35 (m, 1H), 2.32 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H), 2.09 (m, 1H), 2.04 (s, 3H).

ESI-MS m/z: Calcd.. for $C_{40}H_{42}N_4O_{10}S$: 770.7. Found $(M+H)^+$: 771.2

Example 22



To a solution of **21** (22 mg, 0.042 ml) in CH_2Cl_2 (0.8 ml) was added phthalic anhydride (6.44 mg, 0.042 ml) and the reaction mixture was stirred for 2h at 23 °C. Then, carbonyldiimidazole (1mg, 0.006 ml) was added and the mixture was stirred at 23 °C for 7h. Then, carbonyldiimidazole (5.86mg, 0.035 ml) was added and the reaction was stirred at 23 °C for an additional 17h. The solution was diluted with CH_2Cl_2 (15 ml) and washed with 0.1 N HCl (15 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 2:1) to afford **27** (26.4 mg, 96%) as a white solid.

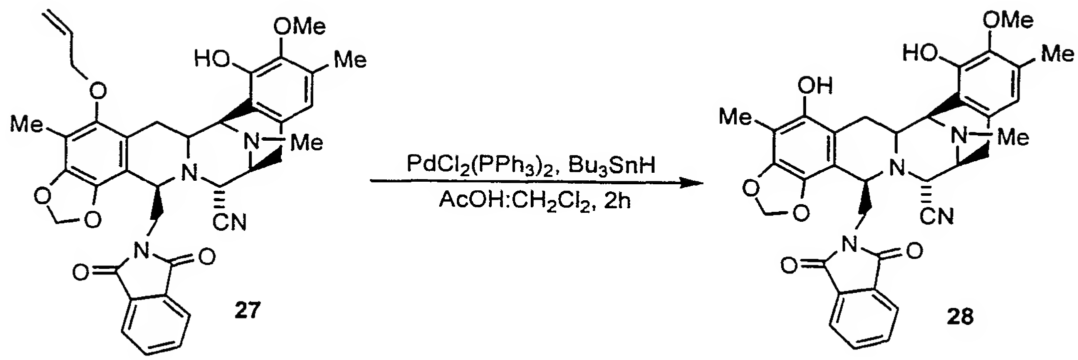
Rf: 0.58 (ethyl acetate).

^{1}H NMR (300 MHz, $CDCl_3$): 7.73–7.64 (m, 4H), 6.40 (s, 1H), 6.12-6.01 (m, 1H), 5.63 (s, 1H), 5.58 (d, J= 1.5 Hz, 1H), 5.37 (dd, J_1= 1.8 Hz, J_2= 17.4 Hz), 5.23 (dd, J_1= 1.8 Hz, J_2= 10.5 Hz, 1H), 5.12 (d, J= 1.5 Hz, 1H), 4.22-4.15 (m, 3H), 4.08 (d, J= 1.8 Hz, 1H), 3.68 (s, 3H), 3.59-3.55 (m 2H), 3.35 (d, J= 8.1 Hz, 1H), 3.27-3.16 (m, 2H), 3.05 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.64 (d, J= 18.0Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 2.09 (s, 3H), 1.80 (dd, J_1= 11.4 Hz, J_2= 15 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.7, 148.9, 146.4, 144.2, 142.6, 139.5, 134.0, 133.5, 132.0, 131.0, 128.3, 123.0, 121.3, 120.9, 118.1, 117.5, 116.8, 113.6, 112.4, 100.8, 74.5, 60.6, 60.5, 57.7, 56.6, 55.6, 55.5, 42.3, 41.7, 26.6, 25.5, 15.9, 9.46.

ESI-MS m/z: Calcd. for $C_{37}H_{35}N_4O_7$: 648.79. Found $(M+H)^+$: 649.3.

Example 23



To a solution of **27** (26 mg, 0.041 ml) in CH_2Cl_2 (11 ml), acetic acid (11 ml), $(PPh_3)_2PdCl_2$ (2.36 mg) and Bu_3SnH (28 ml, 0.10 ml) were added at 23 °C. After stirring at that temperature for 2h the reaction was poured into a pad of flash column (SiO_2, gradient Hex to hexane:ethyl acetate 2:1) to afford **28** (24.7 mg, 99 %) as a white solid.

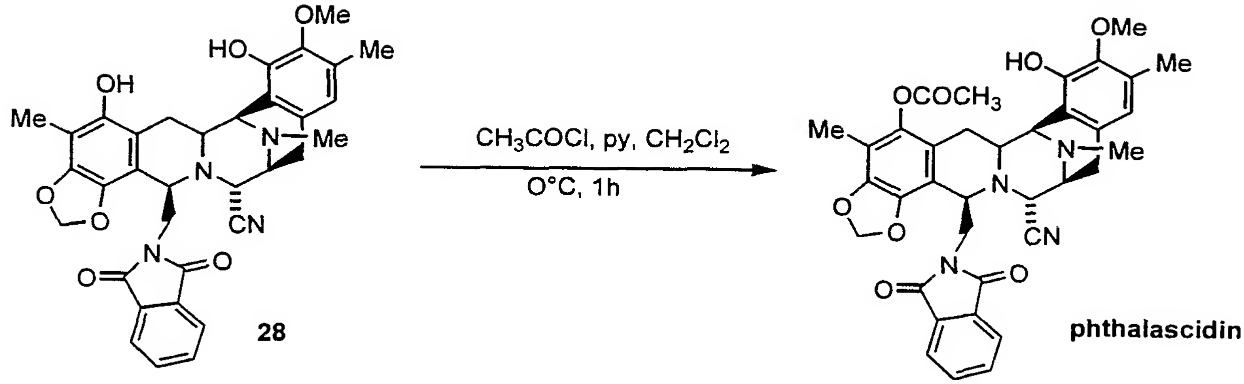
Rf: 0.33 (hexane:ethyl acetate 2:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75-7.70 (m, 2H), 7.69-7.65 (m, 2H), 6.39 (s, 1H), 5.82 (bs, 1H), 5.50 (d, J= 1.5 Hz, 1H), 5.0 (d, J= 1.5 Hz, 1H), 4.45 (bs, 1H), 4.23-4.19 (m, 2H), 4.10-4.09 (m, 1H), 3.73 (s, 3H), 3.60-3.48 (m, 2H), 3.36-3.33 (m, 1H), 3.26-3.20 (m, 1H), 3.14-3.08 (m, 1H), 3.98 (d, J= 14.4 Hz, 1H), 2.61 (d, J= 18.3 Hz, 1H), 2.30 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H), 1.85 (dd, J_1= 12 Hz, J_2= 15.3 Hz);

^{13}C NMR (75 MHz, $CDCl_3$): δ 167.8, 146.4, 145.1, 143.9, 142.7, 137.1, 133.5, 131.9, 130.8, 128.4, 122.9, 120.8, 118.0, 116.8, 114.0, 113.4, 106.4, 100.4, 60.6, 60.5, 57.8, 56.6, 55.5, 55.2, 42.6, 41.5, 25.6, 25.5, 15.8, 8.9.

ESI-MS m/z: Calcd. for $C_{34}H_{32}N_4O_7$: 608.6. Found $(M+H)^+$: 609.2.

Example 24



To a solution of **28** (357 mg, 0.058 ml) in CH_2Cl_2 (3 ml), acetyl chloride (41.58 ml, 0.58 ml) and pyridine (47.3 ml, 0.58 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (15 ml) and washed with 0.1 N HCl (15 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN:H_2O 60:40) to afford phthalascidin (354 mg, 94%) as a white solid.

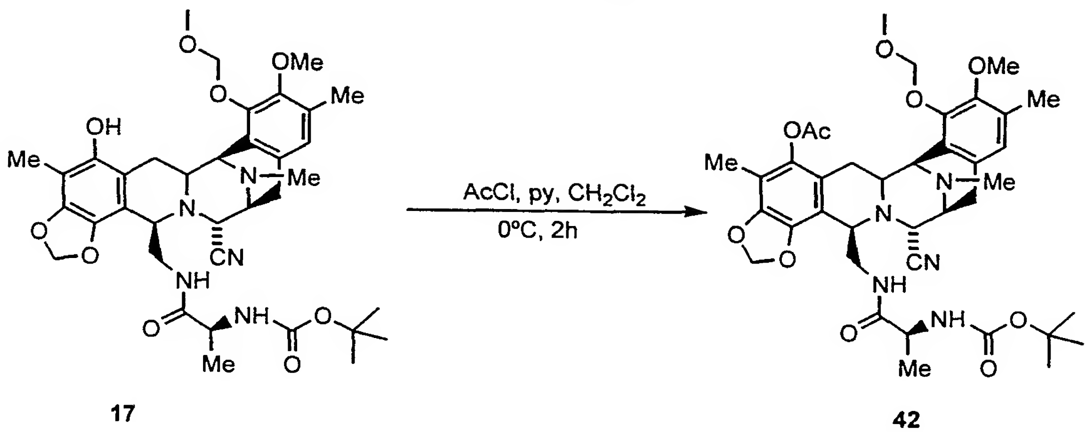
Rf: 0.37 (CH_3CN:H_2O 7:3, RP-18).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.68 (m, 2H), 7.67-7.63 (m, 2H), 6.38 (s, 1H), 5.69 (d, J= 1.2 Hz, 1H), 5.64 (d, J= 1.2Hz, 1H), 5.30 (bs, 1H), 4.25-4.21 (m, 2H), 4.02 (d, J= 2.1 Hz, 1H), 3.64-3.62 (m, 5H), 3.33 (d, J= 8.4 Hz, 1H), 3.21-3.16 (m, 1H), 3.02 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.76 (dd, J_1= 1.8 Hz, J_2= 15.6 Hz, 1H), 2.63 (d, J= 17.7 Hz, 1H), 2.29 (s, 3H), 2.28 (s,3H), 2.21 (s, 3H), 2.0 (s, 3H), 1.73 (dd, J_1= 12.0 Hz, J_2= 15.3 Hz, 1H))

^{13}C NMR (75 MHz, $CDCl_3$)): δ 168.5, 167.6, 146.2, 144.2, 142.5, 141.0, 140.5, 133.4, 131.8, 130.7, 128.2, 120.9, 120.8, 117.9, 116.4, 113.6, 101.1, 60.4, 60.0, 57.0, 56.3, 55.6, 55.4, 41.6, 41.5, 26.5, 25.2, 20.2, 15.7, 9.4.

ESI-MS m/z: Calcd. for $C_{36}H_{34}N_4O_8$: 650. Found $(M+H)^+$: 651.2.

Example 25



To a solution of **17** (300 mg, 0.432 ml) in CH_2Cl_2 (2 ml), acetyl chloride (30.7 ml, 0.432 ml) and pyridine (34.9 ml, 0.432 ml) were added at 0 °C. The reaction mixture was stirred for 2h at that temperature and then, the solution was diluted with CH_2Cl_2 (15 ml) and washed with 0.1 N HCl (15 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to afford **42** (318 mg, 100%) as a white solid that was used in subsequent reactions with no further purification.

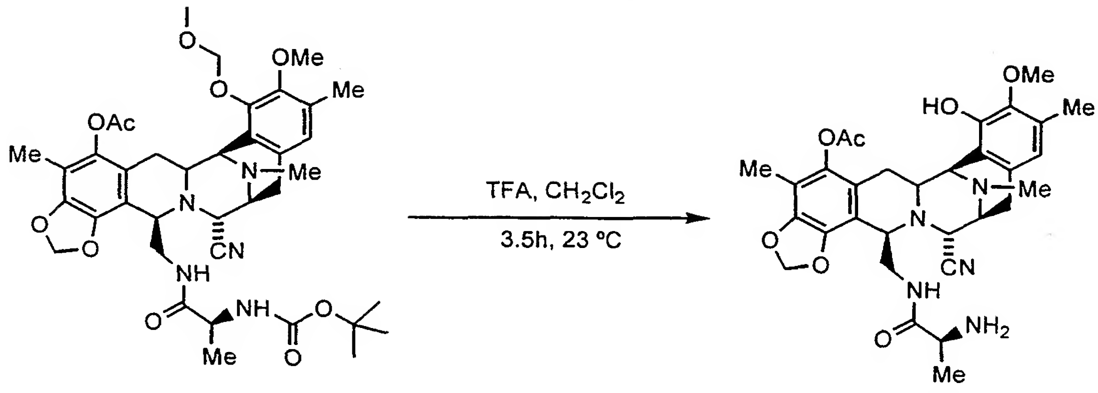
Rf: 0.5 (ethyl acetate:methanol 5:1).

^{1}H NMR (300 MHz, $CDCl_3$). δ 6.66 (s, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.83 (d, J= 1.2 Hz, 1H), 5.42 (t, J= 6.6 Hz, 1H), 5.07 (d, J= 5.7 Hz, 1H), 4.98 (d, J= 5.7 Hz, 1H), 4.16 (d, J= 1.8 Hz, 1H), 4.11 (d, J= 2.7 Hz, 1H), 3.98 (bs, 1H), 3.73-3.61 (m, 2H), 3.64 (s, 3H), 3.52-3.48 (m, 1H), 3.50 (s, 3H), 3.33 (d, J= 9.6 Hz, 1H), 3.17-3.14 (m, 1H), 2.97-2.87 (m, 1H), 2.75-2.70 (d, J= 16.8 Hz, 1H), 2.26 (s, 6H), 2.16 (s, 3H), 1.96 (s, 3H), 1.70 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H), 1.33 (s, 9H), 0.59 (d, J= 6.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)): δ 172.0, 168.3, 162.3, 148.2, 144.4, 140.4, 140.2, 130.9, 130.5, 125.3, 123.4, 120.8, 117.6, 112.7, 111.7, 101.4, 99.1, 79.2, 59.5, 58.8, 57.5, 57.4, 56.4, 55.5, 55.0, 41.3, 39.0, 28.2, 26.4, 24.6, 19.9, 18.4, 15.4, 9.1.

ESI-MS m/z: Calcd. for $C_{38}H_{49}N_5O_{10}$: 735.82. Found $(M+H)^+$: 736.3.

Example 26



42

43

To a solution of **42** (318 mg, 0.432 ml) in CH_2Cl_2 (2.16 ml), trifluoroacetic acid (1.33 ml, 17.30 ml) was added and the reaction mixture was stirred for 3.5h at 23 °C. The reaction was quenched at 0 °C with saturated aqueous sodium bicarbonate (60 ml) and extracted with CH_2Cl_2 (2 x 70 ml). The combined organic layers were dried (sodium sulphate) and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, ethyl acetate:methanol 20:1) to afford **43** (154 mg, 60%) as a white solid.

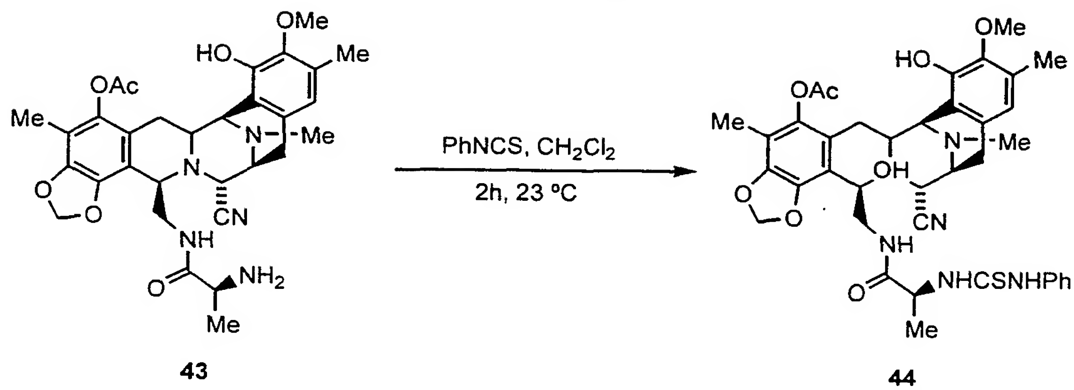
Rf: 0.22 (ethyl acetate:methanol 5:1).

^1H NMR (300 MHz, $CDCl_3$). δ 6.47 (s, 1H), 6.22 (bs, 1H), 5.95 (d, *J*= 1.2 Hz, 1H), 5.88 (d, *J*= 1.2 Hz, 1H), 4.08-4.06 (m, 2H), 4.01 (bs, 1H), 3.69 (s, 3H), 3.49 (d, *J*= 3.6 Hz, 1H), 3.33 (d, *J*= 8.1 Hz, 1H), 3.26-3.22 (m, 1H), 2.95 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.80-2.76 (m, 2H), 2.58 (d, *J*=18Hz, 1H), 2.29 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H), 1.96 (s, 3H), 1.77 (dd, J_1= 12.3 Hz, J_2= 15.6 Hz, 1H), 0.90 (d, *J*=6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)): δ 174.8, 169.0, 146.8, 144.4, 142.8, 140.5, 140.2, 131.1, 128.8, 120.8, 120.5, 117.1, 112.9, 111.6, 101.5, 60.3, 59.0, 56.5, 56.3, 55.6, 55.1, 50.2, 41.6, 39.5, 26.8, 26.3, 24.9, 20.2, 15.4, 9.2.

ESI-MS m/z: Calcd. for $C_{31}H_{37}N_5O_7$: 591.65. Found $(M+H)^+$: 592.3.

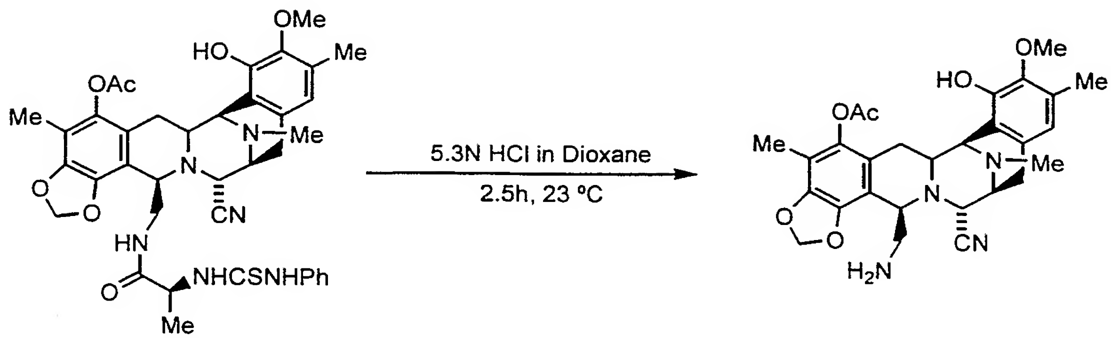
Example 27



To a solution of **43** (154 mg, 0.26 ml) in CH_2Cl_2 (1.3 ml), phenyl isothiocyanate (186 ml, 1.56 ml) was added and the mixture was stirred at 23° C for 2h. The reaction was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient Hexane to hexane:ethyl acetate 1:1) to afford **44** (120 mg, 63 %) as a white solid.

Rf: 0.41 (ethyl acetate:methanol 5:1).
^{1}H NMR (300 MHz, $CDCl_3$). δ 8.17 (s, 1H), 7.49-7.44 (m, 3H), 7.31-7.24 (m, 3H), 7.05 (d, *J*= 6.9 Hz, 1H), 5.98 (d, *J*= 1.2 Hz, 1H), 5.87 (d, *J*= 1.2 Hz, 1H), 5.52 (bs, 1H), 4.54 (t, *J*= 6.6 Hz, 1H), 4.15 (d, *J*= 2.1 Hz, 1H), 4.03 (d, *J*= 2.7 Hz, 2H), 3.80 (bs, 1H), 3.66 (s, 3H), 3.40 (bs, 1H), 3.32 (d, *J*= 7.8 Hz, 1H), 3.16 (d, *J*= 11.7 Hz, 1H), 2.82-2.61 (m, 3H), 2.29 (s, 3H), 2.20 (s, 3H), 2.01 (s, 3H), 1.99 (s, 3H), 1.80 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H), 0.62 (d, *J*= 6.0 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 171.9, 168.7, 146.7, 144.5, 142.6, 140.6, 140.3, 136.3, 131.0, 129.9, 128.9, 126.7, 124.4, 120.9, 120.6, 117.7, 116.6, 112.7, 111.9, 101.4, 60.4, 58.7, 57.5, 56.1, 55.7, 55.1, 53.3, 41.4, 38.8, 26.3, 24.4, 20.2, 18.1, 15.3, 9.2.
ESI-MS m/z: Calcd. for $C_{38}H_{42}N_6O_7S$: 726.3. Found $(M+H)^+$: 727.3.

Example 28



44

45

To a solution of **44** (120 mg, 0.165 ml) in dioxane (0.9 ml), 5.3N HCl/dioxane (1.8 ml) was added and the reaction was stirred at 23 °C for 2.5h. Then, CH_2Cl_2 (10 ml) and H_2O (5 ml) were added to this reaction and the organic layer was decanted. The aqueous phase was basified with saturated aq sodium bicarbonate (20 ml) (pH = 8) at 0 °C and then, extracted with CH_2Cl_2 (2x15 ml). The combined organic extracts were dried (sodium sulphate), and concentrated *in vacuo* to afford **45** (75 mg, 87%) as a white solid that was used in subsequent reactions with no further purification.

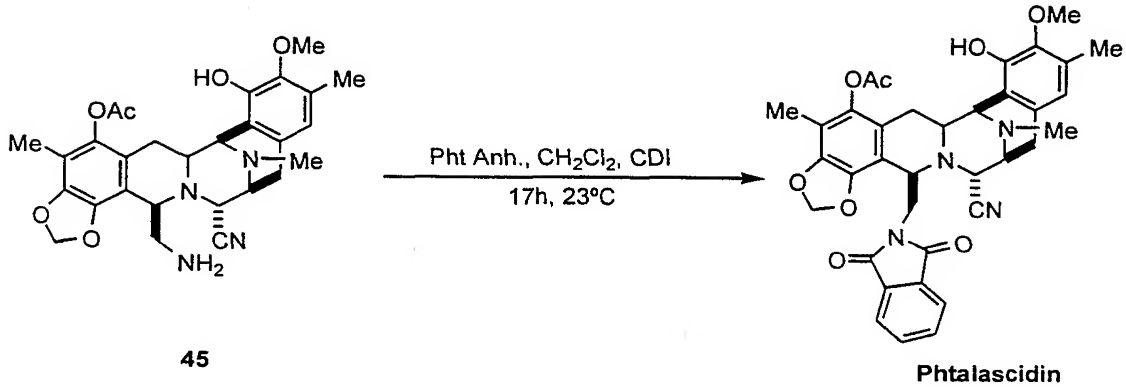
Rf: 0.23 (ethyl acetate:methanol 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.43 (s, 1H), 5.94 (d, J= 1.2 Hz, 1H), 5.87 (d, J= 1.2Hz, 1H), 4.10 (d, J= 2.1 Hz, 1H), 3.98 (d, J= 2.4 Hz, 1H), 3.91 (bs, 1H), 3.69 (s, 3H), 3.34-3.25 (m, 2H), 3.05 (dd, J_1= 1.8 Hz, J_2= 8.1 Hz, 1H), 2.80-2.73 (m, 3H), 2.46 (d, J= 18 Hz, 1H), 2.30 (s, 3H), 2.28 (s,3H), 2.20 (s, 3H), 1.98 (s, 3H), 1.79 (dd, J_1= 12.6 Hz, J_2= 16.2 Hz, 1H);

^{13}C NMR (75 MHz, $CDCl_3$)): δ 168.7, 146.7, 144.4, 142.9, 140.4, 130.4, 128.9, 121.1, 120.8, 117.8, 116.8, 113.6, 111.5, 101.4, 67.6, 60.5, 59.8, 58.4, 56.6, 55.8, 55.3, 43.6, 41.8, 31.3, 25.6, 20.2, 15.6, 9.2.

ESI-MS m/z: Calcd. for $C_{28}H_{32}N_4O_6$: 520.58. Found $(M+H)^+$: 521.3.

Example 29



To a solution of **45** (10 mg, 0.02 ml) in CH_2Cl_2 (0.4 ml) was added phthalic anhydride (2.84 mg, 0.02 ml) and the reaction mixture was stirred for 2 h at 23 °C. Then, carbonyldiimidazole (0.5 mg, 0.003 ml) was added and the mixture was stirred at 23 °C for 7h. Then, carbonyldiimidazole (2.61 mg, 0.016 ml) was added and the reaction was stirred at 23 °C for an additional 17h. The solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, $CH_3CN:H_2O$ 60:40) to afford phthalascidin (11.7 mg, 93%) as a white solid.

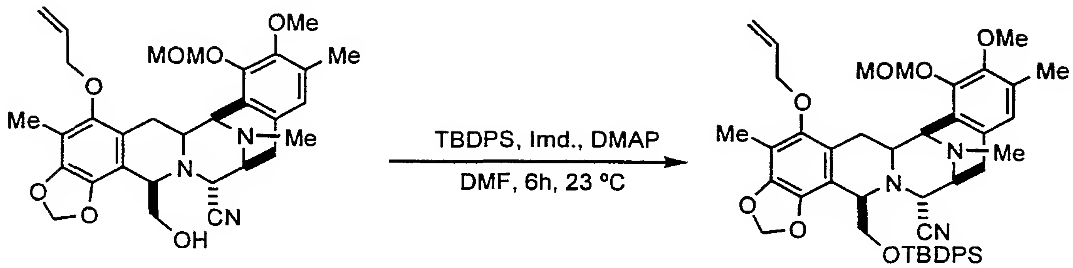
Rf: 0.37 ($CH_3CN:H_2O$ 7:3, RP-18).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.68 (m, 2 h), 7.67-7.63 (m, 2 h), 6.38 (s, 1H), 5.69 (d, J= 1.2 Hz, 1H), 5.64 (d, J= 1.2 Hz, 1H), 5.30 (bs, 1H), 4.25-4.21 (m, 2 h), 4.02 (d, J= 2.1 Hz, 1H), 3.64-3.62 (m, 5H), 3.33 (d, J= 8.4 Hz, 1H), 3.21-3.16 (m, 1H), 3.02 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.76 (dd, J_1= 1.8 Hz, J_2= 15.6 Hz, 1H), 2.63 (d, J= 17.7 Hz, 1H), 2.29 (s, 3H), 2.28 (s,3H), 2.21 (s, 3H), 2.0 (s, 3H), 1.73 (dd, J_1= 12.0 Hz, J_2= 15.3 Hz, 1H));

^{13}C NMR (75 MHz, $CDCl_3$)): δ 168.5, 167.6, 146.2, 144.2, 142.5, 141.0, 140.5, 133.4, 131.8, 130.7, 128.2, 120.9, 120.8, 117.9, 116.4, 113.6, 101.1, 60.4, 60.0, 57.0, 56.3, 55.6, 55.4, 41.6, 41.5, 26.5, 25.2, 20.2, 15.7, 9.4.

ESI-MS m/z: Calcd. for $C_{36}H_{34}N_4O_8$: 650. Found $(M+H)^+$: 651.2.

Example 30



25

26

To a solution of **25** (18 mg, 0.032 ml) in DMF (0.05 ml), cat. DMAP (0.5 mg, 0.004 ml), imidazole (5 mg, 0.08 ml) and *tert*-Butyldiphenylsilyl chloride (12.5 ml, 0.048 ml) were added at 0 °C and the reaction mixture was stirred for 6h at 23 °C. Water (10 ml) was added at 0 °C and the aqueous phase was extracted with hexane:ethyl acetate 1:10 (2 x 10 ml). The organic layer was dried (sodium sulphate), filtered, and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography (SiO_2, hexane:ethyl acetate 3:1) to afford **26** (27 mg, 88 %) as a white solid.

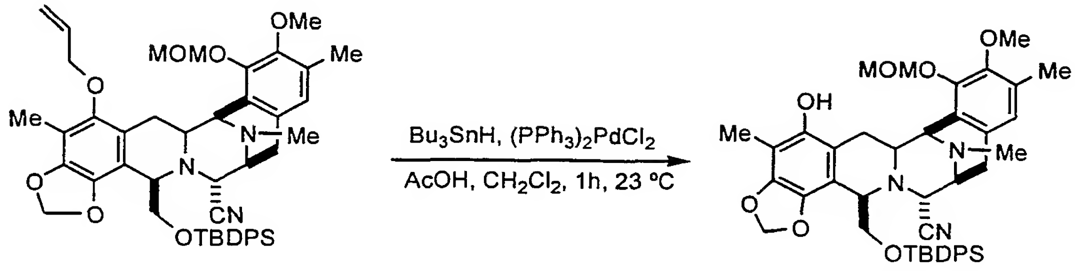
Rf: 0.29 (hexane:ethyl acetate 3:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.58 (m, 2 h), 7.42-7.28 (m, 8H), 6.71 (s, 1H), 6.19-6.02 (m, 1H), 5.78 (d, J= 1.2 Hz, 1H), 5.64 (d, J= 1.2 Hz, 1H), 5.40 (dd, J_1= 1.2 Hz, J_2= 17.1 Hz, 1H), 5.27 (dd, J_1= 1.2 Hz, J_2= 10.2 Hz, 1H), 5.13 (s, 2 h), 4.45 (d, J= 2.4 Hz, 1H), 4.24 (d, J= 2.1 Hz, 1H), 4.17-4.06 (m, 3H), 3.75 (s, 3H), 3.64 (dd, J_1= 2.4 Hz, J_2= 9.9 Hz, 1H), 3.59 (s, 3H), 3.42-3.21 (m, 4H), 3.10 (dd, J_1= 8.1 Hz, J_2= 17.7 Hz, 1H), 2.70 (d, J= 17.7 Hz, 1H), 2.33 (s, 3H), 2,26 (s, 3H), 2.11 (s, 3H), 2.08-1.89 (m, 1H), 0.87 (s, 9H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 148.3, 148.1, 144.0, 139.0, 135.6, 135.4, 133.8, 133.1, 132.6, 130.5, 130.3, 129.6, 129.4, 127.5, 127.4, 125.1, 124.3, 121.6, 118.5, 117.5, 112.9, 111.7, 100.8, 99.2, 74.0, 67.7, 61.5, 59.6, 59.0, 57.7, 57.1, 55.4, 41.6, 29.6, 26.6, 25.5, 18.8, 15.8, 9.2.

ESI-MS m/z: Calcd. for $C_{47}H_{55}N_3O_7Si$: 801.3. Found $(M+H)^+$: 802.3.

Example 31



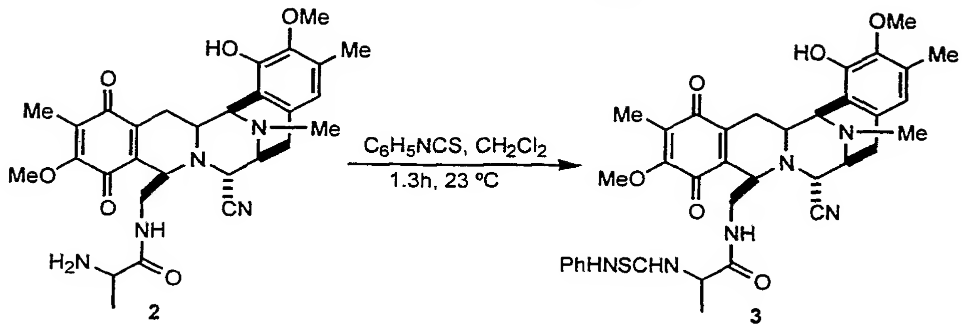
26

ET-11

To a solution of **26** (7 mg, 0.0087 ml) in CH_2Cl_2 (0.15 ml), acetic acid (2.5 ml, 0.044 ml), $(PPh_3)_2PdCl_2$ (0.5 mg, 6.96 x 10^{-4} ml) and Bu_3SnH (3.5 ml, 0.013 ml) were added at 23 °C. The reaction mixture was stirred at that temperature for 1h. The solution was diluted with a mixture of hexane:ethyl acetate 5:1 (0.5 ml) and poured into a pad of flash column (SiO_2, gradient 5:1 to 1:1 hexane:ethyl acetate) affording **ET-11** (5 mg, 75 %) as a white solid.

Rf: 0.36 (hexane:ethyl acetate 1:5, silica).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (m, 2 h), 7.41-7.25 (m, 8H), 6.67 (s, 1H), 5.72 (d, J= 1.0 Hz, 1H), 5.58 (d, J= 1.0 Hz, 1H), 5.51 (s, 1H), 5.38 (d, J= 5.75 Hz, 1H), 5.16 (d, J= 5.7 Hz, 1H), 4.57 (d, J= 2.9 Hz, 1H), 4.21 (m, 1H), 4.09 (m, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.68 (dd, J_1= 2.1 Hz, J_2= 10.4 Hz, 1H), 3.38-3.26 (m, 3H), 3.11 (dd, J_1= 2.5 Hz, J_2= 15.7 Hz, 1H), 3.01 (dd, J_1= 8.9 Hz, J_2= 17.9 Hz, 1H), 2.70 (d, J= 17.9 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.06 (s, 3H), 1.89 (dd, J_1= 12.1 Hz, J_2= 15.7 Hz, 1H), 0.9 (s, 9H).);
^{13}C NMR (75 MHz, $CDCl_3$): δ 149.0, 147.4, 145.3, 144.3, 136.3, 135.7, 135.4, 133.2, 130.9, 130.5, 129.6, 129.5, 127.5, 125.0, 118.6, 112.5, 112.1, 105.7, 100.5, 99.8, 68.5, 61.5, 59.7, 58.8, 57.7, 56.9, 56.5, 55.4, 41.7, 26.6, 26.2, 25.5, 18.9, 15.8, 14.2, 8.7.
ESI-MS m/z: Calcd. for $C_{44}H_{51}N_3O_7Si$: 761. Found $(M+H)^+$: 762.

Example 32



A solution of **2** (3.0 g, 5.46 ml) and phenyl isothiocyanate (3.92mL. 32.76 ml) in CH_2Cl_2 (27 ml) was stirred at 23° C for 1.5h. The reaction mixture was partitioned between CH_2Cl_2 (10 ml) and H_2O (5 ml). The organic layer was dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, gradient Hex to 2:3 hexane:ethyl acetate) to give **3** (3.29 g, 88%) as a yellow solid.

Rf: 0.27 (ACN:H_2O 3:2, RP-C18);

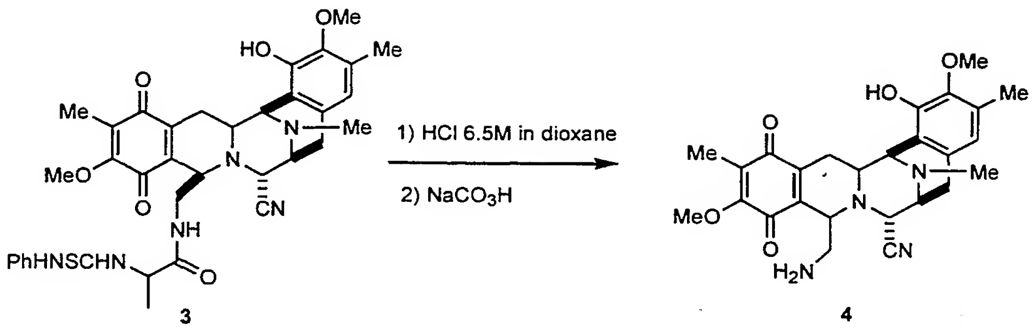
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (bs, 1H), 7.42-7.11 (m, 5H), 6.65 (d, 1H), 6.29 (s, 1H), 5.6-5.5 (m, 1H), 4.19-4.14 (m, 2 h), 4.08 (d, 1H), 3.92 (s, 3H), 3.87-3.65 (m, 6H), 3.77 (s, 3H), 3.37-2.98 (m, 8H), 2.50 (d, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 1.96 (d, 1H), 1.87 (s, 3H), 1.81-1.75 (m, 1H), 0.96 (d, 3H);

^{13}C NMR (75 MHz,

$CDCl_3$):δ 185.7, 180.9, 178.9, 172.0, 155.7, 147.1, 143.2, 142.4, 136.0, 135.1, 130.5, 129.9, 129.3, 128.5, 126.9, 124.4, 120.2, 117.4, 116.3, 77.1, 60.9, 58.6, 56.2, 55.8, 55.0, 54.6, 53.5, 41.7, 40.3, 25.1, 24.5, 18.4, 15.8, 8.7

ESI-MS m/z: Calcd. for $C_{36}H_{40}N_6O_6S$: 684.8. Found $(M+H)^+$: 685.2.

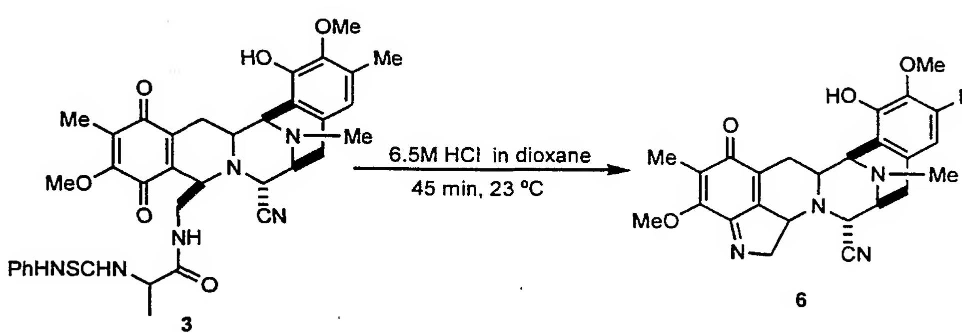
Example 33



A solution of **3** (0.143 g, 0.208 ml) in 6.5 M HCl/dioxane (150 ml) was stirred at 23 °C for 6h. Then, toluene (3 ml) was added to this reaction and the organic layer was decanted. The residue was partitioned between saturated aqueous sodium bicarbonate (3 ml) and $CHCl_3$ (3x3 ml) The organic layers were dried and concentrated to afford title compound as a mixture of **4** and **6** (**4**:**6** 90:10) which slowly cyclizes to **6** on standing.

Rf: 0.4 (ethyl acetate:methanol5:1, silica);
^1H NMR (300 MHz, $CDCl_3$): δ 6.45 (s, 1H), 4.16 (m, 1H), 4.02 (d, 1H), 3.96 (s, 3H), 3.79 (m, 2 h), 3.75 (s, 3H), 3.35 (m, 1H), 3.20-3.00 (m, 3H), 2.87 (d, 1H), 2.75 (d, 1H), 2.43 (d, 1H), 2.34 (s, 3H), 2.30 (s, 3H), 1.93 (s, 3H), 1.72-1.5 (m, 3H);
ESI-MS m/z: Calcd. for $C_{26}H_{30}N_4O_5$: 478.5. Found $(M+H)^+$: 479.2

Example 34



A solution of **3** (0.143 g, 0.208 ml) in 6.5M HCl/dioxane (150 ml) was stirred at 23 °C for 1h. Evaporation of the solvent gave a residue which was purified by flash column chromatography (ethyl acetate/methanol/triethylamine 100:25:0.1) to give **6** (80 mg, 83%) as

a yellow solid.

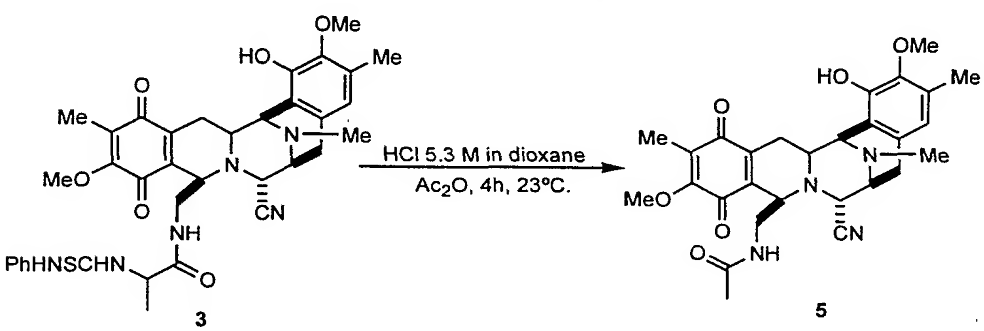
Rf: 0.26 (ACN:H_2O 3:2, RP-C18);

^1H NMR (500 MHz, $CDCl_3$): δ 6.46 (s, 1H), 5.9 (bs, 1H) 4.67 (dd, J=18.3 Hz, J= 7.8 Hz, 1H), 4.24 (d, 1H), 4.16 (s, 3H), 3.93 (d, J=2.7 Hz, 1H), 3.8 (m, 2 h), 3.77 (s, 3H), 3.45 (m, 2 h), 3.08 (dd, J=17.9 Hz, J=3.6 Hz, 1H), 2.78 (m, 1H), 2.55 (d, 1H), 2.3 (m, 1H), 2.3 (s, 3H), 2. 28 (s, 3H), 1.90 (s, 3H);

^{13}C NMR (75 MHz,$CDCl_3$):δ 186.2, 162.1, 154.9, 146.9, 145.3, 143.0, 130.1, 129.4, 128,1, 125.0, 121.4, 116.4, 116.2, 66.6, 60.7, 60.7, 60.1, 59.6, 58.8, 55.6, 54.9, 41.9, 25.3, 24.7, 15.7, 8.9.

ESI-MS m/z: Calcd. for $C_{26}H_{28}N_4O_4$: 460.5. Found $(M+H)^+$: 461.1

Example 35



To a solution of **3** (2.38 g, 3.47 ml) in dioxane (5 ml) 5.3M HCl in dioxane (34 ml) was added and the reaction was stirred at 23 °C for 45 minutes. Then Ac_2O (51 ml, 539.5 ml) was added and the mixture was stirred for 4h. The reaction was cooled at 0 °C and partitioned between aqueous saturated Na_2CO_3 (300 ml) and ethyl acetate (300 ml) at this temperature. The organic phase was dried over sodium sulphate, filtered and concentrated. The residue was purified by flash column chromatography (SiO_2, gradient CH_2Cl_2 to CH_2Cl_2:ethyl acetate 1:2) to give **5** (1.75 g, 97%) as a yellow solid.

Rf: 0.53 (ACN:H_2O 3:2, RP-C18);

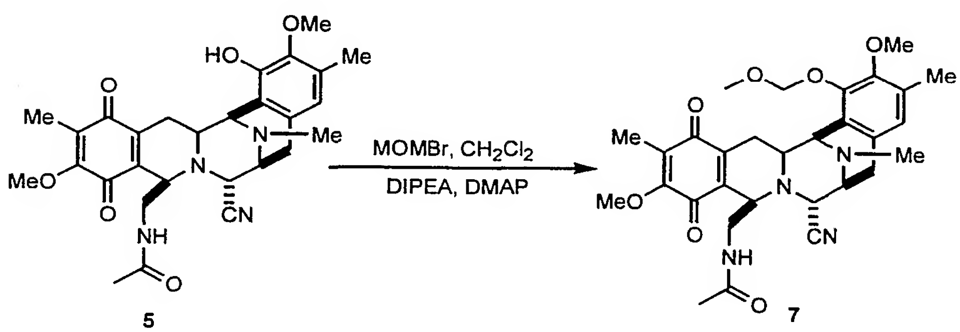
^1H NMR (300 MHz, $CDCl_3$): δ 6.51 (s, 1H), 5.98 (bs, 1H), 4.84 (dd, 1H), 4.17 (d, 1H), 4.00

(d, 1H), 3.99 (s, 3H), 3.85 (bs, 1H), 3.81 (m, 1H), 3.74 (s, 3H), 3.70 (d, 1H), 3.23 (m, 1H), 3.11 (dd, 1H), 3.09 (m, 1H), 2.93 (m, 2 h), 2.44 (d, 1H), 3.67 (s, 3H), 2.25 (s, 3H), 1.70 (s, 3H), 1.60-1.50 (m, 2 h), 1.29 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9, 180.8, 169.9, 160.2, 156.2, 147.0, 143.1, 140.4, 136.1, 130.6, 129.6, 127.9, 120.4, 117.2, 61.0, 60.7, 58.6, 56.1, 55.7, 55.1, 54.3, 41.8, 41.1, 25.7, 23.9, 22.2, 15.7, 8.7.

ESI-MS m/z: Calcd. for $C_{28}H_{32}N_4O_6$: 520.6. Found $(M+H)^+$: 521.1

Example 36



To a solution of **5** (1.75 g, 3.36 ml) in CH_2Cl_2 (17 ml) diisopropylethylamine (11.71 ml, 67.23 ml), DMAP (20 mg, 0.17 ml) and bromomethyl methyl ether (4.11 ml, 50.42 ml) were added at 0 °C. After 6 h at 23 °C the reaction was partitioned between CH_2Cl_2 (50 ml) and aqueous saturated sodium bicarbonate (25 ml). The organic layer was dried over sodium sulphate and the solvent was eliminated under reduced pressure. The crude was purified by flash column chromatography (RP-18, CH_3CN/H_2O 1/1) to give **7** (1.32 g, 70%) as a yellow solid.

Rf: 0.34 (ACN:H_2O 2:3, RP-C18);

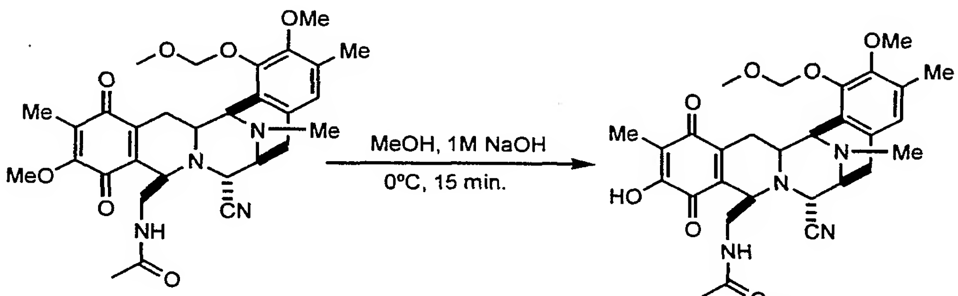
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 5.14 (s, 2 h), 4.82 (m, 1H), 4.22 (d, 1H), 4.00 (s, 3H), 4.0 (m, 1H), 3.83 (m, 2 h), 3.7 (s, 3H), 3.58 (s, 3H), 3.4 (m, 1H), 3.2-2.95 (m, 6H), 2.43 (d, 1H), 2.37 (s, 3H), 2.22 (s, 3H), 1.89 (s, 3H), 1.5-1.4 (m, 2 h), 1.31 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.9, 180.7, 169.6, 156.2, 148.9, 148.5, 140.3, 136.2, 131.3, 130.1, 127.7, 124.6, 123.7, 117.3, 99.5, 99.2, 60.9, 59.7, 58.8, 57.7, 56.4, 55.7, 55.0, 54.2,

51.0, 41.6, 41.0, 40.5, 25.5, 23.9, 22.3, 19.3, 15.6, 14.6, 8.6.

ESI-MS m/z: Calcd. for $C_{30}H_{36}N_4O_7$: 564.6. Found $(M+H)^+$: 565.3

Example 37



7

8

To a solution of 7 (0.37 g, 0.65 ml) in methanol (74 ml) at 0 °C was added 1M sodium hydroxide (130 ml). The reaction was stirred for 15 minutes and then, quenched at 0 °C with 6M HCl to pH = 5. The mixture was extracted with ethyl acetate (3 x 50 ml) and the combined organic layers were dried over sodium sulphate and concentrated *in vacuo*. The residue was purified by flash column chromatography (RP-C18 $CH_3CN:H_2O$ 1/:1) to afford **8** (232 mg, 65%) as a yellow oil.

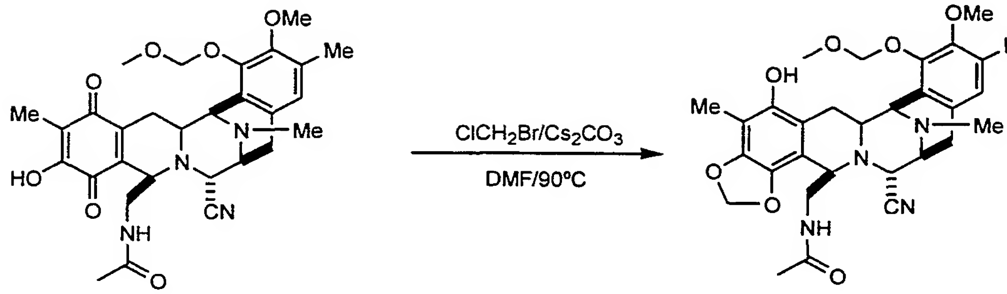
Rf: 0.5 (ACN:H_2O 3:2, RP-C18);

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (s, 1H), 5.15 (s, 2 h), 4.86 (m, 1H), 4.26 (d, 1H),), 4.01 (d, 1H), 3.88-3.81 (m, 2 h), 3.70 (s, 3H), 3.58 (s, 3H), 3.39 (m, 1H), 3.27-3.21 (m, 1H), 3.18-3.08 (m, 2 h), 3.03-2.97 (m, 1H) 2.47 (d, 1H), 2.37 (s, 3H), 2. 22 (s, 3H), 1.90 (s, 3H), 1.57-1.46 (m, 2 h), 1.33 (s, 3H);

^{13}C NMR (75 MHz, $CDCl_3$): δ 185.3, 180.6, 175.9, 170.1, 151.5, 148.9, 148.6, 143.3, 133.7, 131.5, 129.9, 124.7, 123.5, 117.1, 117.0, 99.2, 59.8, 58.7, 57.8, 56.3, 55.3, 54.9, 54.3, 41.5, 40.7, 29.6, 25.5, 24.4, 22.2, 20.7, 15.7, 8.0.

ESI-MS m/z: Calcd. for $C_{29}H_{34}N_4O_7$: 550.6. Found $(M+H)^+$: 551.2

Example 38

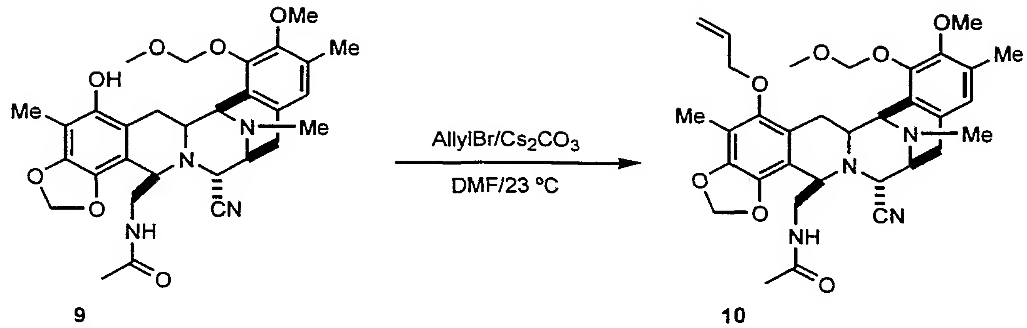


8 9

To a degassed solution of compound **8** (240mg, 0.435 ml) in DMF (30 ml) 10 % Pd/C (48 mg) was added and the reaction was stirred under H_2 (atmospheric pressure.) for 1h. The reaction was filtered through a pad of celite under Argon to a Schlenk tube, as a colourless solution, containing anhydrous Cs_2CO_3 (240 mg, 0.739 ml). Then, bromochloromethane (0.566 ml, 8.71 ml) was added. The tube was sealed and stirred at 90 °C for 3h. The reaction was cooled and filtrated through celite and washed with CH_2Cl_2. The organic layer was concentrated and dried (sodium sulphate) to afford **9** as a brown oil that was used in the next step with no further purification.

Rf: 0.36 (SiO_2, hexane:ethyl acetate 1:5)
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.71 (s, 3H), 5.89 (d, 1H), 5.81 (d, 1H), 5.63 (bs, 1H), 5.33 (d, 1H), 5.17 (d, 1H), 4.97 (m, 1H), 4.20 (d, 1H), 4.09 (m, 1H), 3.99 (m, 1H), 3.68 (m, 1H), 3.65 (s, 6H), 3.59-3.47 (m, 4H), 3.37-3.27 (m, 2 h), 3.14- 2.97 (m, 2 h), 2.62 (d, 1H), 2.32 (s, 3H), 2.20 (s, 3H), 2.08 (s, 3H), 1.72 (m, 1H), 1.36 (s, 3H);
^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 149.1, 147.4, 145.5, 136.2, 130.9, 130.8, 125.0, 122.9, 117.7, 112.6, 111.8, 106.4, 100.8, 99.8, 59.8, 58.9, 57.7, 56.6, 56.4, 55.5, 55.2, 41.6, 40.1, 29.6, 25.9, 25.0, 22.6, 15.6, 8.8.
ESI-MS m/z: Calcd. for $C_{30}H_{36}SiN_4O_7$: 564.6. Found $(M+H)^+$: 565.3.

Example 39



To a flask containing **9** (245 mg, 0.435 ml) in DMF, (4 ml), cesium carbonate (425 mg, 1.30 ml) and allyl bromide (376 ml, 4.35 ml) were added at 0 °C and the mixture was stirred at 23 °C for 1h. The reaction was filtered though a pad of celite and partitioned between CH_2Cl_2 (25 ml) and H_2O (10 ml). The organic phase was dried (sodium sulphate) and concentrated at reduced pressure to afford a residue that was purified by flash column chromatography (SiO_2, $CHCl_3$:ethyl acetate 1:2) to give **10** as a yellow oil. (113 mg, 43 %).

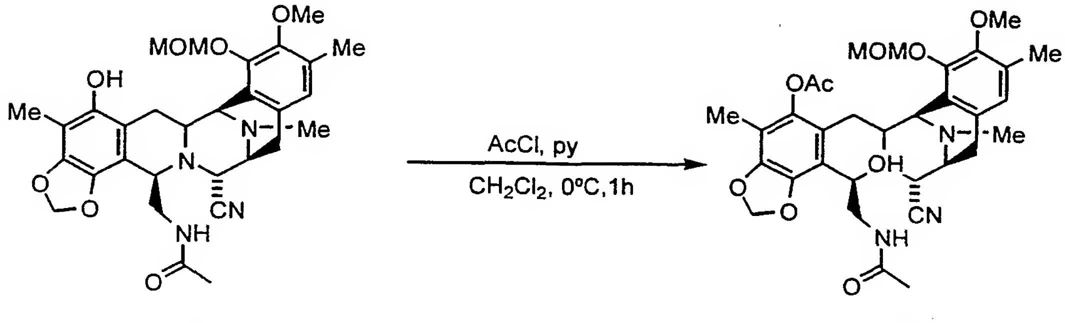
Rf: 0.36 (hexane:ethyl acetate 1:5)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.3-6.0 (m, 1H), 5.94 (d, 1H), 5.87 (d, 1H), 5.43-5.36 (m, 2 h), 5.22 (s, 2 h), 5.00 (m, 1H), 4.22 (m, 1H), 4.17-4.01 (m, 1H), 3.98 (m, 2 h), 3.71-3.67 (m, 1H), 3.69 (s, 3H), 3.62-3.51 (m, 3H), 3.58 (s, 3H), 3.39-3.37 (m, 1H), 3.31-3.26 (m, 3H), 3.09 (dd, 1H), 2.56 (d, 1H), 2.36 (s, 3H), 2.21 (s, 3H), 2.11 (s, 3H), 2.24-2.10 (m, 1H), 1.82-1.73 (m, 1H), 1.24 (bs, 3H)

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 148.8, 148.3, 139.1, 133.7, 130.9, 130.3, 125.2, 120.2, 117.7, 113.1, 112.6, 101.3, 99.3, 74.1, 59.7, 59.3, 57.8, 57.0, 56.1, 56.1, 55.2, 41.6, 41.0, 40.9, 29.7, 26.3, 22.5, 15.6, 9.3

ESI-MS m/z: Calcd. for $C_{33}H_{40}N_4O_7$: 604.7. Found $(M+H)^+$: 605.3.

Example 40



9 46

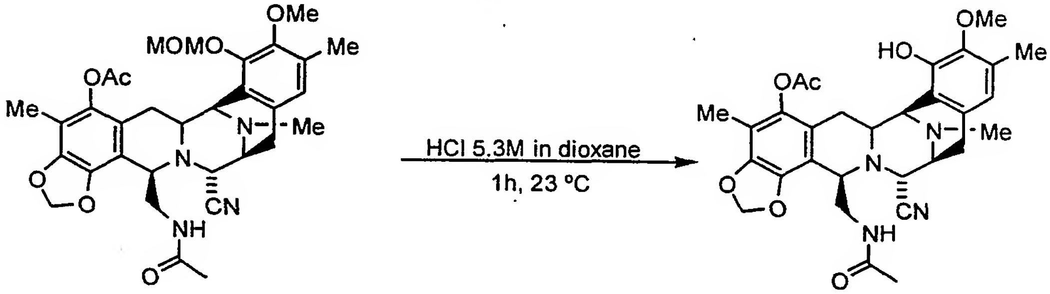
To a solution of **9** (22 mg, 0.039 ml) in CH_2Cl_2 (0.2 ml), acetyl chloride (2.79 ml, 0.039 ml) and pyridine (3.2 ml, 0.039 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to afford **46** (22 mg, 93%) as a white solid.

Rf: 0.4 (hexane:ethyl acetate 1:5).

^{1}H NMR (300 MHz, $CDCl_3$). δ 6.74 (s, 1H), 5.97 (d, J= 0.9 Hz, 1H), 5.91 (d, J= 0.9 Hz, 1H), 5.12 (d, J= 5.7 Hz, 2 h), 5.04 (d, J= 5.7 Hz, 1H) 4.90 (t, J= 6 Hz, 1H), 4.17 (d, J= 2.7 Hz, 1H), 4.05 (d, J= 2.7 Hz, 1H), 4.01 (bs, 1H), 3.71 (s, 3H), 3.57 (s, 3H), 3.50-3.44 (m, 2 h), 3.38-3.36 (m, 1H), 3.30-3.26 (m, 1H), 3.00 (dd, J_1= 7.8 Hz, J_2= 18.0 Hz, 1H), 2.79 (d, J= 12.9 Hz, 1H), 2.60 (d, J=18.0 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H), 1.68 (dd, J_1=11.7 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{32}h_{38}N_4O_8$: 606.67. Found $(M+H)^+$: 607.3.

Example 41



46 47

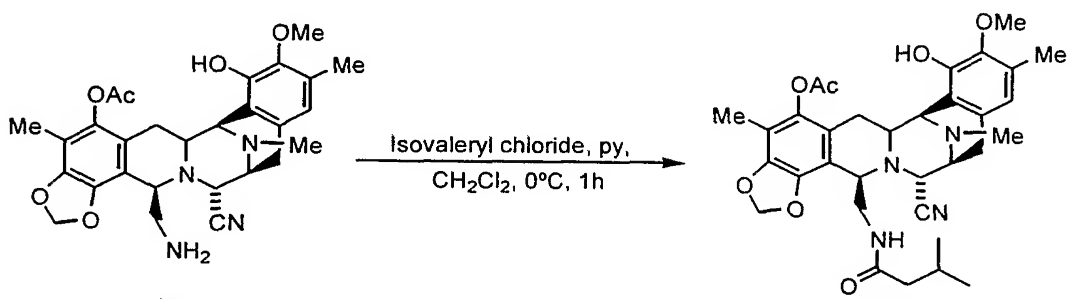
To a solution of **46** (8 mg, 0.013 ml) in dioxane (0.1 ml), 5.3N HCl/dioxane (0.5 ml) was added and the reaction was stirred at 23 °C for 1h. Then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to afford **47** (5 mg. 70%) as a white solid.

Rf: 0.4 (hexane:ethyl acetate 1:5).

^{1}H NMR (300 MHz, $CDCl_3$). δ 6.51 (s, 1H), 5.97 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 4.97 (bs, 1H), 4.11 (bs, 1H), 4.04-4.02 (m, 2 h), 3.75 (s, 3H),), 3.65 (d, J= 2.1 Hz, 2 h), 3.56-3.30 (m, 2 h), 3.04 (dd, J_1= 7.5 Hz, J_2= 18 Hz, 1H), 2.80 (d, J= 14.4 Hz. 1H), 2.59 (d, J= 18.3 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H), 1.76 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H), 1.33 (s, 3H), 1.25 (s, 3H).

ESI-MS m/z: Calcd. for $C_{30}H_{34}N_4O_7$: 562.61. Found $(M+H)^+$: 563.3.

Example 42



45 48

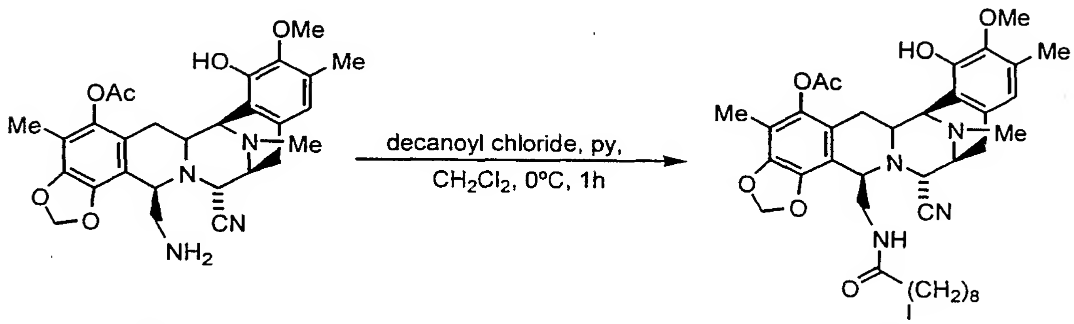
To a solution of **45** (10 mg, 0.0192 ml) in CH_2Cl_2 (0.3 ml), isovaleryl chloride (2.34 ml, 0.0192 ml) and pyridine (1.55 ml, 0.0192 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 1:2) to afford **48** (11 mg, 95%) as a white solid.

Rf: 0.12 (Hex: ethyl acetate 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 5.98 (d, J= 1.5Hz, 1H), 5.91(d, J= 1.5 Hz, 1H), 5.75 (s, 1H), 5.02 (t, J= 5.4 Hz, 1H), 4.10 (d, J= 1.5 Hz, 1H), 4.06 (d, J= 2.7 Hz, 1H), 4.02 (d, J= 2.7 Hz, 1H), 3.77 (s, 3H), 3.76-3.71 (m, 1H), 3.86-3.28 (m, 3H), 3.04 (dd, J_1= 8.1 Hz, J_2= 18.3Hz, 1H), 2.78 (d, J=15.9 Hz, 1H), 2.55 (d, J=18 Hz, 1H), 2.32 (s, 6H), 2.26 (s, 3H), 1.98 (s, 3H), 1.84-1.68 (m, 2 h), 1.36 (d, J= 7.2 Hz, 2 h), 0.69 (d, J= 6.6 Hz, 3H), 0.62 (d, J=6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{33}H_{40}N_4O_7$: 604.69. Found $(M+H)^+$: 605.3.

Example 43



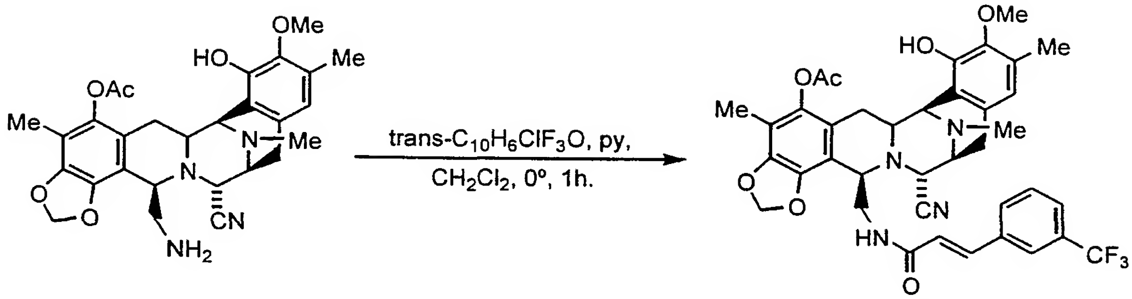
To a solution of **45** (10 mg, 0.0192 ml) in CH_2Cl_2 (0.3 ml), isovaleryl chloride (3.98 ml, 0.0192 ml) and pyridine (1.55 ml, 0.0192 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 1:2) to afford **49** (12.4 mg, 96%) as a white solid.

Rf: 0.7 (ethyl acetate:methanol10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.50 (s, 1H), 5.98 (d, J= 1.5Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.73 (s, 1H), 5.08 (t, J= 5.4 Hz, 1H), 4.10 (d, J= 1.5 Hz, 1H), 4.05 (m., 1H), 4.01 (m, 1H), 3.76 (s, 3H), 3.65-3.61 (m, 1H), 3.40-3.27 (m, 3H), 3.03 (dd, J_1= 8.1 Hz, J_2= 18.6 Hz, 1H), 2.78 (d, J=13.2 Hz, 1H), 2.57 (d, J=18.3 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 1.99 (s, 3H), 1.79 (dd, J_1= 12.0 Hz, J_2= 16.5 Hz, 1H), 1.73-1.42 (m, 4H), 1.33-1.18 (m, 10H), 1.03 (m, 2 h), 0.87 (t, J= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{38}H_{50}N_4O_7$: 674.83. Found $(M+H)^+$: 675.5.

Example 44



45

50

To a solution of **45** (14.5 mg, 0.0278 ml) in CH_2Cl_2 (0.3 ml), trans-3-trifluoromethyl cinnamoyl chloride (4.76 ml, 0.0278 ml) and pyridine (2.25 ml, 0.0278 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 1:1) to afford **50** (18.7 mg, 94%) as a white solid.

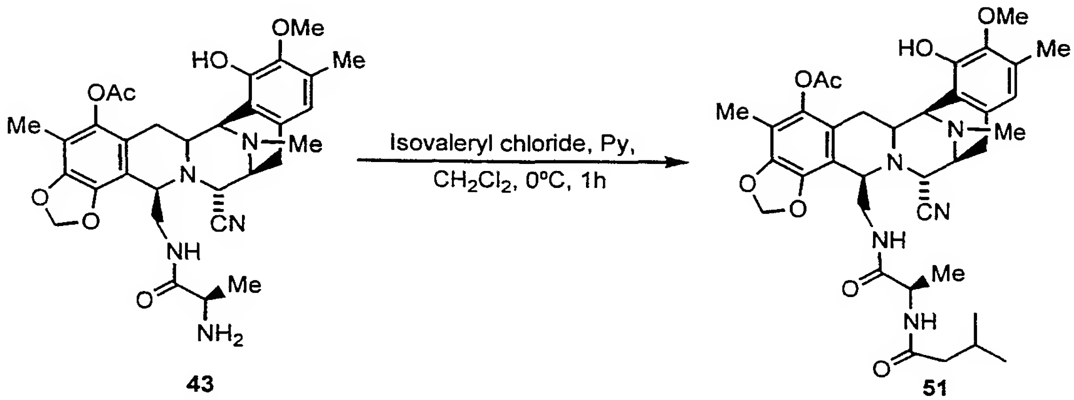
Rf: 0.64 (ethyl acetate:methanol5:1).

^{1}H NMR (300 MHz, CH_3OD). δ 7.74-7.55 (m, 4H), 7.23 (d, *J*= 16.0 Hz, 1H), 6.34 (s, 1H), 6.12 (d, *J*= 16.0 Hz, 1H), 6.07 (d, *J*= 0.9 Hz, 1H), 5.96 (d, *J*= 0.9 Hz, 1H), 4.39 (d, *J*= 2.4 Hz, 1H), 4.07-4.05 (m, 1 H), 3.81 (bs, 1H), 3.46-3.51 (m, 3H), 3.42 (s, 3H), 3.09 (br d, *J*= 12.0 Hz, 1H), 2.94-2.85 (m, 2 h), 2.74 (d, *J*=18.3 Hz, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 2.02 (s, 3H), 1.80 (s, 3H), 1.84-1.75 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$)): δ 168.7, 165.3, 146.5, 144.7, 142.6, 140.6, 138.0, 135.9, 131.0, 130.9, 129.1, 128.6, 125.8, 125.7, 124.5, 124.4, 122.7, 121.2, 117.8, 116.5, 113.0, 112.0, 101.7, 60.4, 59.1, 56.5, 56.4, 55.6, 55.3, 41.8, 40.3, 26.6, 25.1, 20.3, 15.4, 9.3.

ESI-MS m/z: Calcd. for $C_{38}H_{37}F_3N_4O_7$: 718.72. Found $(M+H)^+$: 719.3.

Example 45



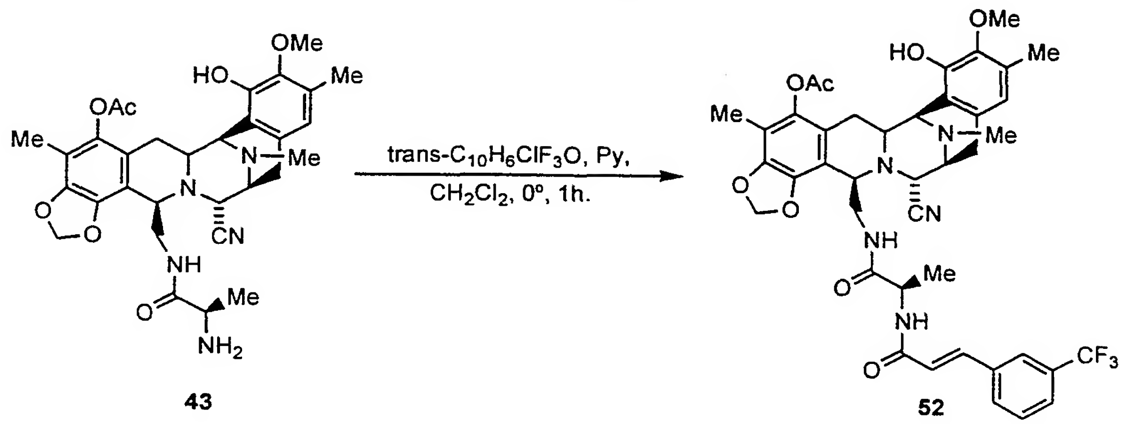
To a solution of **43** (33 mg, 0.0557 ml) in CH_2Cl_2 (0.4 ml), isovaleryl chloride (6.79 ml, 0.0557 ml) and pyridine (4.5 ml, 0.0557 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 1:2) to afford **51** (34 mg, 91%) as a white solid.

Rf: 0.09 (Hex: ethyl acetate 1:2).

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.46 (s,1H), 6.10 (bs, 1H), 5.99 (d, *J*= 0.9Hz, 1H), 5.90 (d, *J*= 0.9 Hz, 1H), 5.30 (t, *J*= 6.0 Hz, 1H), 4.10-4.05 (m, 3H),3.81 (bs, 1H), 3.74 (s, 3H), 3.54 (bs,1H), 3.38-3.36 (m, 1H), 3.29-3.21 (m, 1H), 3.00 (dd, J_1= 8.0 Hz, J_2= 18.0 Hz, 1H), 2.25 (s, 3H), 2.20 (s, 3H), 2.00 (s, 3H), 1.95-1.90 (m, 3H), 0.87 (d, *J*=6.6 Hz, 6H), 0.76 (d, *J*=6.0 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{36}H_{45}N_5O_8$: 675.77. Found $(M+H)^+$: 676.3.

Example 46



To a solution of **43** (33 mg, 0.0557 ml) in CH_2Cl_2 (0.4 ml), trans-3-trifluoromethyl cinnamoyl chloride (9.52 ml, 0.0557 ml) and pyridine (4.5 ml, 0.0557 ml) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 1:2) to afford **52** (40 mg, 92%) as a white solid.

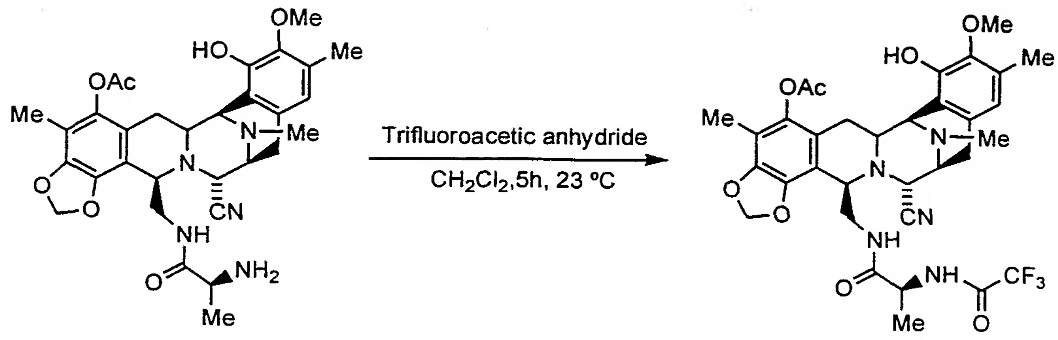
Rf: 0.21 (hexane:ethyl acetate 1:2).

^{1}H NMR (300 MHz, CD_3OD). δ 7.74-7.47 (m, 4H), 6.49 (s, 1H), 6.40 (d, J= 15.6 Hz, 1H), 6.00 (d, J= 1.5 Hz, 1H), 5.90 (d, J= 1.5 Hz, 1H), 5.47 (t, J= 6 Hz, 1H), 4.12-4.09 (m, 3H), 3.93 (bs, 1H), 3.71 (s, 3H), 3.59-3.58 (m, 1H), 3.38 (d, J=7.8 Hz, 1H), 3.29 (d, J=12.0 Hz, 1H), 3.00 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.79-2.78 (m, 1H), 2.65 (d, J=18.3 Hz, 1H) 2.29 (s, 6H), 2.28 (s, 3H), 2.22 (s, 3H), 1.84-1.80 (m, 1H), 0.85-0.84 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 168.8, 164.4, 146.9, 144.6, 143.0, 140.5, 140.5, 139.3, 135.7, 131.1, 131.0, 129.4, 129.1, 126.0, 124.1, 124.0, 122.4, 121.1, 120.7, 120.6, 117.7, 116.9, 112.8, 112.0, 101.6, 60.6, 59.3, 57.1, 56.3, 55.9, 55.2, 49.0, 41.7, 49.9, 26.5, 25.1, 20.2, 18.4, 15.7, 9.3.

ESI-MS m/z: Calcd. for $C_{41}H_{42}F_3N_5O_8$: 789.8. Found $(M+H)^+$: 790.3.

Example 47



43 53

To a solution of **43** (10 mg, 0.0169 ml) in CH_2Cl_2 (0.2 ml) trifluoroacetic anhydride (2.38μl, 0.0169 ml) was added at 23 °C. The reaction mixture was stirred for 5h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 3:2) to afford **53** (10.7 mg, 93%) as a white solid.

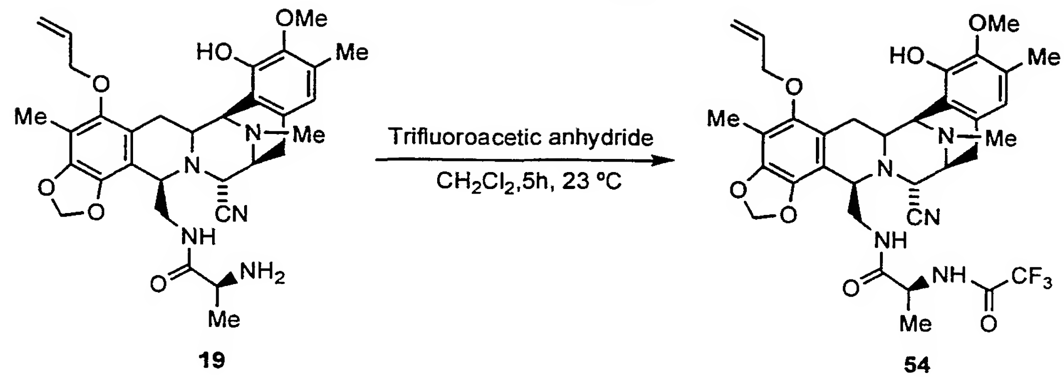
Rf: 0.57 (ethyl acetate:methanol5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H), 6.00 (d, J= 1.2 Hz, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.87 (bs, 1H), 5.32 (bs, 1H), 4.12(d, J= 2.1 Hz, 1H), 4.08 (d, J= 1.8 Hz, 1H), 3.78-3.56 (m, 3H), 3.72 (s, 3H), 3.40 (d, J= 8.1 Hz, 1H), 3.25 (d, J= 9.3 Hz, 1H), 3.00 (dd, J_1= 8.4 Hz, J_2= 18.0 Hz, 1H), 2.77 (dd, J_1= 2.1 Hz, J_2= 15.9 Hz, 1H), 2.68 (d, J= 18.6 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.00 (s, 3H), 1.75 (dd, J_1= 11.4 Hz, J_2= 15.9 Hz, 1H), 0.69 (d, J= 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 168.6,156.0, 147.0, 144.6, 143.0, 140.6, 140.4, 131.0, 129.4, 120.9, 120.7, 117.6, 116.8, 112.4, 112.1, 101.6, 60.5, 59.0, 57.1, 56.3, 55.6, 55.2, 48.7, 41.6, 39.4, 26.5, 24.9, 20.2, 17.8, 15.4, 9.2.

ESI-MS m/z: Calcd. for $C_{33}H_{36}F_3N_5O_8$: 687.63. Found $(M+H)^+$: 688.66.

Example 48



To a solution of **19** (11 mg, 0.0169 ml) in CH_2Cl_2 (0.2 ml) trifluoroacetic anhydride (2.38 ml, 0.0169 ml) was added at 23 °C. The reaction mixture was stirred for 5h and then, the solution was diluted with CH_2Cl_2 (5 ml) and washed with 0.1 N HCl (3 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: ethyl acetate 3:2) to afford **54** (10.7 mg, 93%) as a white solid.

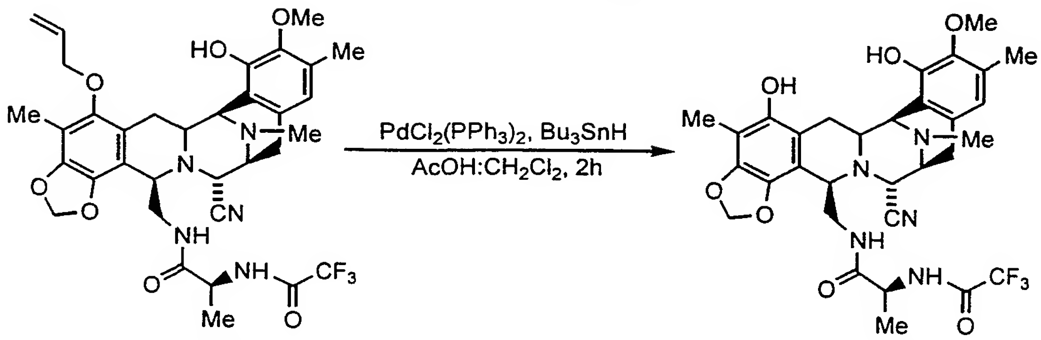
Rf: 0.6 (ethyl acetate:methanol5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (d, *J*= 6.3 Hz, 1H), 6.45 (s, 1H), 6.04 (m, 1H), 5.95 (d, *J*= 1.5 Hz, 1H), 5.84 (d, *J*= 1.5 Hz, 1H), 5.32 (m, 2 h), 5.21 (m, 1H), 4.11 (m, 4H), 3.73 (s, 3H), 3.64 (m, 2 h), 3.51 (m, 1H), 3.37 (d, *J*= 7.8 Hz, 1H), 3.22 (m, 2 h), 3.03 (dd, 1H, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.60 (d, *J*= 18.3 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H), 1.86 (dd, J_1= 12 Hz, J_2= 16.2 Hz, 1H), 0.82 (d, *J*= 7.2 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0, 156.0, 148.4, 147.1, 144.3, 143.0, 138.7, 133.8, 130.5, 129.4, 120.6, 120.4, 117.6, 117.5, 117.0, 113.5, 112.5, 112.4, 101.1, 74.1, 66.8, 60.4, 59.3, 56.9, 56.6, 56.3, 55.4, 48.7, 41.6, 40.1, 26.2, 25.0, 17.6, 15.4, 9.1.

ESI-MS m/z: Calcd. for $C_{35}H_{39}F_3N_5O_7$: 685.69. Found $(M+H)^+$: 686.3.

Example 49



54

55

To a solution of **54** (100 mg, 0.415 ml) in CH_2Cl_2 (4 ml), acetic acid (40 ml), $(PPh_3)_2PdCl_2$ (8.4 mg, 0.012 ml) and Bu_3SnH (157 ml, 0.56 ml) were added at 23 °C. After stirring at that temperature for 2 h the reaction was poured into a pad of flash column (SiO_2, gradient Hex to hexane:ethyl acetate 2:1) to afford **55** (90 mg, 96%) as a white solid.

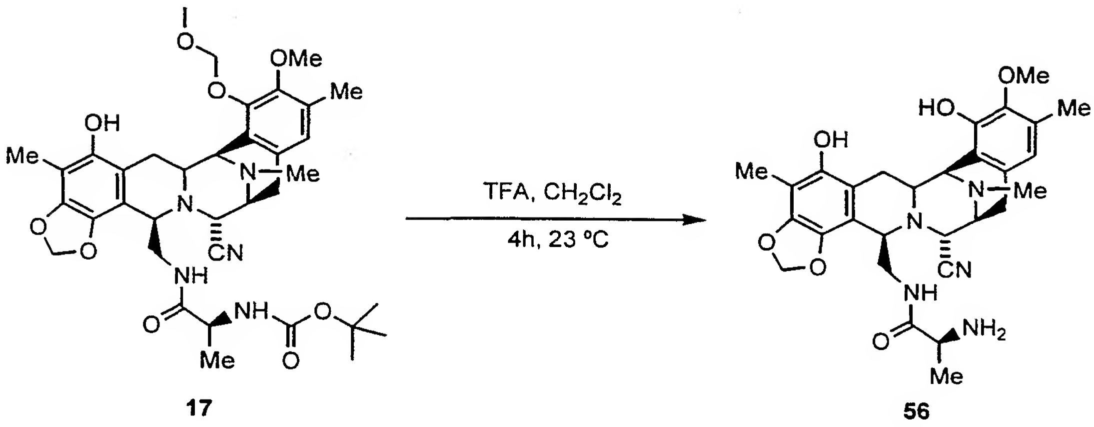
Rf: 0.6 (hexane:ethyl acetate 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J= 7.2 Hz, 1H), 6.45 (s, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.82 (d, J= 1.2 Hz, 1H), 5.37 (t, J= 6.0 Hz, 1H), 4.15 (d, J= 2.1 Hz, 1H), 4.04 (d, J= 1.8 Hz, 1H), 3.70 (s, 3H), 3.66-3.53 (m, 2 h), 3.37-3.31 (m, 2 h), 3.19-3.15 (d, J= 11.7 Hz, 1H), 3.08-3.00 (m, 2 h), 2.56 (d, J=18.3 Hz, 1H), 2.30 (s, 3H), 2.24 (s, 3H), 2.04 (s, 3H), 1.91 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H), 0.84 (d, J= 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 156.3, 147.3, 144.9, 144.4, 143.3, 136.7, 130.7, 129.3, 120.6, 117.6, 117.4, 114.4, 112.1, 107.7, 101.0, 85.8, 60.5, 59.3, 56.5, 56.4, 56.2, 55.2, 48.9, 41.6, 40.9, 25.7, 25.3, 18.0, 15.6, 8.7.

ESI-MS m/z: Calcd. for $C_{32}h_{35}F_3N_5O_7$: 645.63. Found $(M+H)^+$: 646.2.

Example 50



To a solution of **17** (200 mg, 0.288 ml) in CH_2Cl_2 (1.44 ml), trifluoroacetic acid (888 ml, 11.53 ml) was added and the reaction mixture was stirred for 4h at 23 °C. The reaction was quenched at 0 °C with saturated aqueous sodium bicarbonate (60 ml) and extracted with ethyl acetate (2 x 70 ml). The combined organic layers were dried (sodium sulphate) and concentrated *in vacuo* to afford **56** (147 mg, 93%) as a white solid that was used in subsequent reactions with no further purification.

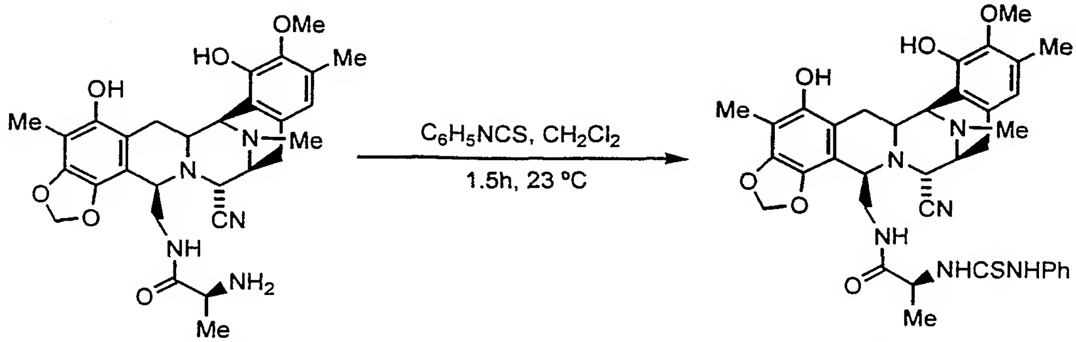
Rf: 0.19 (ethyl acetate:methanol5:1).

^{1}H NMR (300 MHz, CD_3OD). δ 6.48 (s, 1H), 5.88, d, J= 0.9 Hz, 1H), 5.81 (d, J= 0.9 Hz, 1H), 4.35 (d, J= 2.4 Hz, 1H),4.15 (d, J= 1.8 Hz, 1H), 3.99-3.98 (m, 1H), 3.70 (s, 3H), 3.52-2.96 (m, 7H), 2.68 (d, J= 18.3 Hz, 1H), 2.24 (s, 3H), 2.23 (s, 3H), 2.06 (s, 3H), 1.85 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H), 0.91 (d, J= 6.6 Hz, 3H).

^{13}C NMR (75 MHz, CD_3OD): δ 173.2, 149.1, 145.6, 144.9, 138.0, 132.2, 130.6, 121.4, 119.6, 117.4, 114.3, 109.2, 102.5, 82.3, 60.4, 58.4, 58.3, 57.8, 56.6, 50.1, 42.3, 41.6, 27.8, 26.2, 19.5, 15.5, 9.8.

ESI-MS m/z: Calcd. for $C_{29}H_{35}N_5O_6$: 549.62. Found $(M+H)^+$: 550.3.

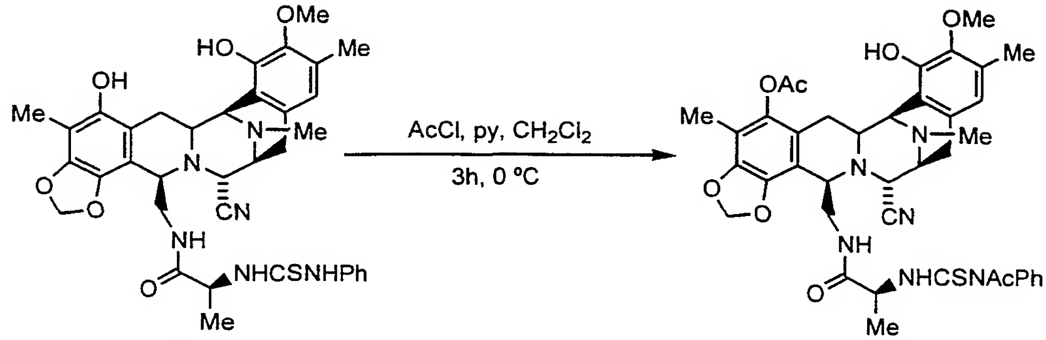
Example 51



To a solution of **56** (10 mg, 0.018 ml) in CH_2Cl_2 (0.4 ml), phenyl isothiocyanate (13 ml, 0.109 ml) was added and the reaction was stirred at 23° C for 1.5h. The mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (SiO_2, gradient Hexane to 1:1 hexane:ethyl acetate) to afford **57** (8 mg, 65%) as a white solid.

Rf: 0.57 (ethyl acetate:methanol10:1).
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (bs, 1H), 7.41-7.36 (m, 2 h), 7.27-7.22 (m, 1H), 7.02-7.00 (d, *J*= 7.8 Hz, 2 h), 6.71 (d, *J*= 7.2 Hz, 1H), 6.31 (s, 1H), 6.17 (bs, 1H), 5.93 (d, *J*=1.2 Hz, 1H), 5.83 (d, *J*= 1.2 Hz, 1H), 5.55 (bs, 1H), 5.20-5.17 (m, 1H), 4.16 (d, *J*= 1.8 Hz, 1H), 4.05 (bs, 1H), 4.02 (d, *J*= 2.4 Hz, 1H), 3.79 (s, 3H), 3.75-3.71 (m, 1H), 3.35 (d, *J*= 7.8 Hz, 1H), 3.28-3.19 (m, 2 h), 3.12-2.97 (m, 2 h), 2.50 (d, *J*=18.3 Hz, 1H), 2.32 (s, 3H), 2.21 (s, 3H), 2.15-2.09 (dd, J_1= 11.4 Hz, J_2= 15.9 Hz, 1H), 1.95 (s, 3H), 0.88 (d, *J*=6.9 Hz, 3H).
^{13}C NMR (75 MHz, $CDCl_3$): δ 178.5, 171.7, 147.2, 145.0, 144.3, 143.3, 137.0, 135.7, 130.6, 130.4, 129.6, 127.5, 124.3, 120.6, 117.7, 117.2, 115.3, 112.1, 108.3, 100.9, 60.9, 59.5, 56.7, 56.5, 56.2, 55.2, 54.1, 41.7, 41.1, 26.3, 25.4, 18.5, 15.8, 9.0.
ESI-MS m/z: Calcd. for $C_{36}H_{40}N_6O_6S$: 684.81. Found $(M+H)^+$: 685.3.

Example 52



57 58

To a solution of **57** (45 mg, 0.065 ml) in CH_2Cl_2 (0.5 ml), acetyl chloride (4.67 ml, 0.065 ml) and pyridine (5.3 ml, 0.065 ml) were added at 0 °C. The reaction mixture was stirred for 3h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 40:60) to afford **58** (14 mg, 28%) as a white solid.

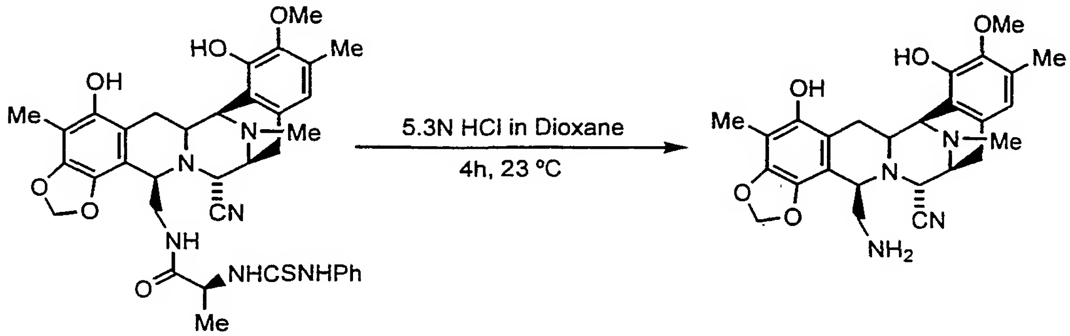
Rf: 0.34 (CH_3CN: H_2O 7:15).

^1H NMR (300 MHz, $CDCl_3$). δ 11.90 (d, *J*= 6.6 Hz, 1H), 7.45-7.40 (m, 3H), 7.18-7.15 (m, 2 h), 6.58 (s, 1H), 6.00 (d, *J*= 1.2 Hz, 1H), 5.89 (d, *J*= 1.2 Hz, 1H), 5.70 (s, 1H), 5.37 (t, *J*= 4.8 Hz, 1H), 4.48 (m, 1H), 4.23 (bs, 1H), 4.07 (bs, 2 h), 3.85-3.75 (m, 1H), 3.70 (s, 3H), 3.46-3.41 (m, 2 h), 3.24-3.20 (m, 1H), 3.00-2.95 (m, 1H), 2.87-2.75 (m, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H), 1.85 (dd, J_1= 11.4 Hz, J_2= 15.6 Hz, 1H), 1.66 (s, 3H), 0.82 (d, *J*= 6.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)): δ 182.6, 174.3, 171.0, 146.6, 144.6, 142.7, 142.3, 140.7, 140.2, 131.3, 129.8, 129.3, 128.9, 128.8, 121.5, 120.4, 117.3, 116.6, 112.8, 112.0, 111.3, 101.5, 60.5, 59.0, 57.6, 56.2, 55.9, 55.3, 55.1, 41.6, 39.4, 27.8, 26.5, 24.8, 20.2, 17.1, 15.5, 9.3.

ESI-MS m/z: Calcd. for $C_{40}H_{44}N_6O_8S$: 768.88. Found $(M+H)^+$: 769.2.

Example 53



57

59

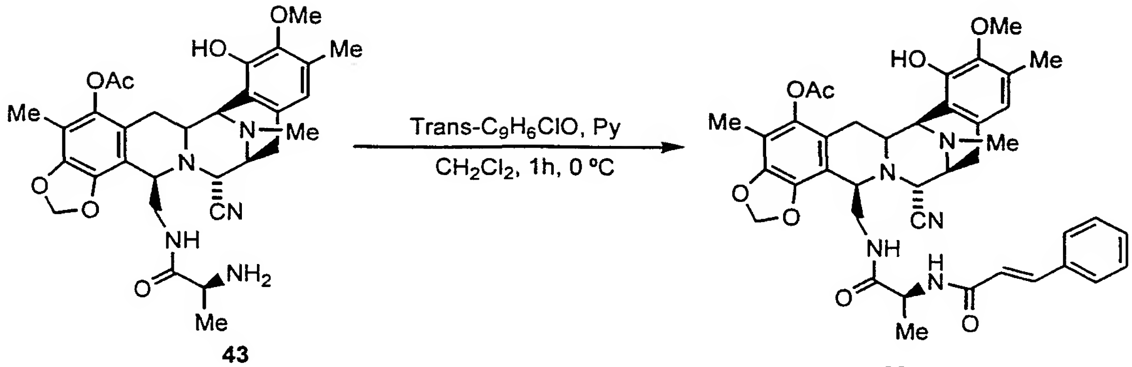
A solution of **57** (130 mg, 0.189 ml) in dioxane (1 ml), 5.3N HCl/dioxane (1.87 ml) was added and the reaction was stirred at 23 °C for 4h. Then, CH_2Cl_2 (15 ml) and H_2O (10 ml) were added to this reaction and the organic layer was decanted. The aqueous phase was basified with saturated aq sodium bicarbonate (60 ml) (pH = 8) at 0 °C and then, extracted with ethyl acetate (2x50 ml). The combined organic extracts were dried (sodium sulphate), and concentrated *in vacuo* to afford **59** (63 mg, 70%) as a white solid.

Rf: 0.15 (ethyl acetate:methanol5:1).

^{1}H NMR (300 MHz, $CDCl_3$). δ 6.67 (s, 1H), 5.99 (d, J= 0.9 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.10 (bs, 1H), 4.32 (d, J= 7.2 Hz, 1H), 4.25 (dd, J_1= 3.6 Hz, J_2= 9.3 Hz, 1H), 3.7 (s, 3H), 3.71-3.64 (m, 2 h), 3.50 (dd, J_1= 2.4 Hz, J_2= 15.9 Hz, 1H), 3.42-3.37 (m, 2 h), 3.16 (dd, J_1=3.6 Hz, J_2= 12.9 Hz, 1H), 2.57 (dd, J_1= 9.3 Hz, J_2= 12.9 Hz, 1H), 2.27 (s, 3H), 2.11 (s, 3H), 1.91 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{26}H_{30}N_4O_5$: 478.5. Found $(M+H)^+$: 479.3.

Example 54



43

60

A solution of **43** (20 mg, 0.0338 mmol) in CH_2Cl_2 (0.3 ml), cinnamoyl chloride (5.63 mg , 0.0338 mmol) and pyridine (2.73 ml, 0.0338 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **60** (22 mg, 90%) as a white solid.

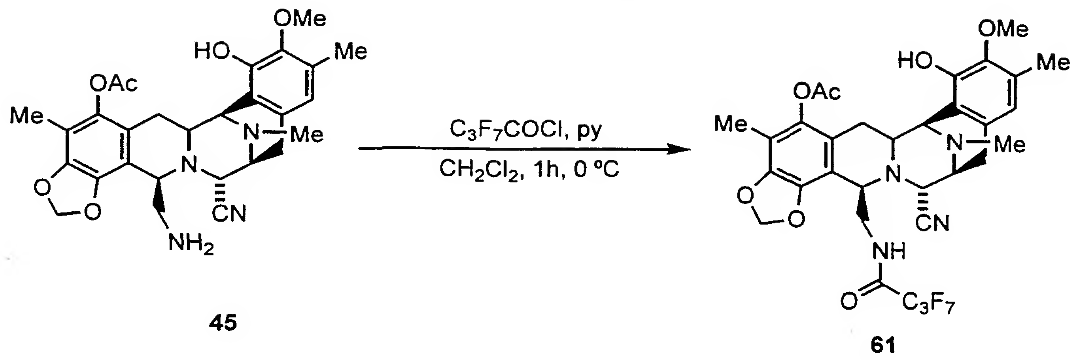
Rf: 0.56 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$). 7.51 (s, 1H), 7.50-7.47 (m, 2H), 7.36-7.35 (m, 2H), 6.43 (s, 1H), 6.36 (brd, J= 15.9 Hz, 2H), 6.01 (d, J= 1.5 Hz, 1H), 5.90 (brd, J= 1.5 Hz, 2H), 5.42 (t, J= 6.0 Hz 1H), 4.12-4.07 (m, 3H), 3.96-3.95 (m, 1H), 3.73 (bs, 3H), 3.58 (bs, 2H), 3.39 (d, J= 8.7 Hz, 1H), 3.25 (d, J= 11.7 Hz, 1H), 3.0 (dd, J_1= 7.5 Hz, J_2= 17.7 Hz, 1H), 2.78 (d, J= 15.9 Hz, 1H), 2.67 (d, J= 16.5 Hz, 1H), 2.29 (s, 6H), 2.23 (s, 3H), 1.99 (s, 3H), 1.82 (dd, J_1= 11.4 Hz, J_2= 15.6 Hz, 1H), 0.83 (d, J= 6.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)): δ. 172.0, 165.0, 146.9, 144.6, 143.1, 141.0, 140.5, 134.8, 131.0, 129.7, 129.1, 128.8, 127.8, 125.5, 123.8, 123.0, 121.1, 120.5, 117.7, 116.9, 112.8, 112.0, 101.9, 60.6, 59.2, 57.1, 56.4, 55.9, 55.3, 48.8, 41.7, 40.0, 26.5, 25.1, 20.3, 18.5, 15.7, 9.3.

ESI-MS m/z: Calcd. for $C_{40}H_{43}N_5O_8$: 721.8. Found $(M+H)^+$: 722.3.

Example 55



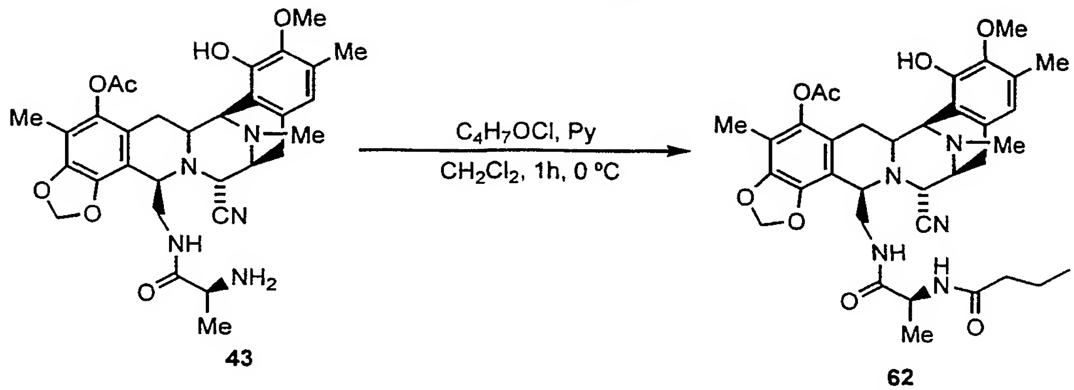
A solution of **45** (19 mg, 0.0364 mmol) in CH_2Cl_2 (0.3 ml), heptafluorobutyryl chloride (5.44 ml, 0.0364 mmol) and pyridine (2.95 ml, 0.0364 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **61** (11.7 mg, 45%) as a white solid.

Rf: 0.76 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.12 (bs, 1H), 5.98 (d, J= 1.2 Hz, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.72 (bs, 1H), 4.13-4.11 (m, 2H), 4.0 (d, J= 2.4 Hz, 1H), 3.98-3.96 (m, 1H), 3.73 (s, 3H), 3.39 (d, J= 7.5 Hz, 1H), 3.39-3.28 (m, 2H), 3.09 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.80 (d, J= 16.2 Hz, 1H), 2.46 (d, J= 18.3 Hz, 1H), 2.32 (s, 6H), 2.21 (s, 3H), 1.99 (s, 3H), 1.80 (dd, J_1= 12.0 Hz, J_2= 16.2 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{32}H_{31}F_7N_4O_7$: 716.6. Found $(M+H)^+$: 717.2.

Example 56



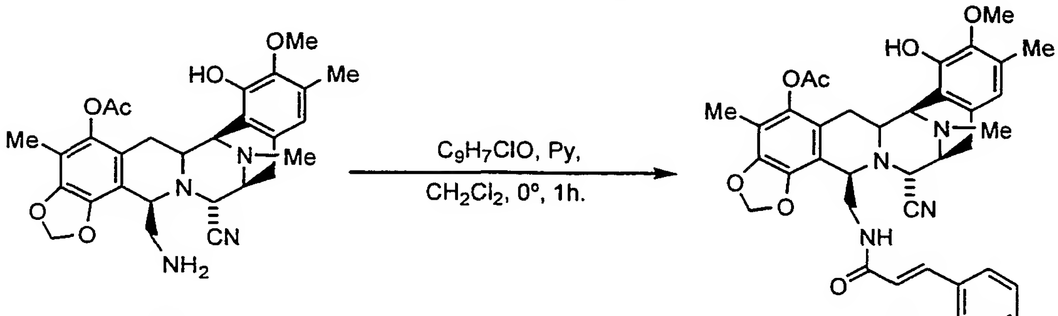
A solution of **43** (24 mg, 0.04 mmol) in CH_2Cl_2 (0.3 ml), butyryl chloride (4.15 ml, 0.04 mmol) and pyridine (3.28 ml, 0.04 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **62** (24 mg, 90%) as a white solid.

Rf: 0.35 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 1H), 6.10 (d, J= 6.5 Hz, 1H), 6.0 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.86 (bs, 1H), 5.31 (d, J= 6.9 Hz, 1H), 4.11-4.06 (m, 3H), 3.85-3.81 (m, 1H), 3.75 (s, 3H), 3.59-3.53 (m, 2H), 3.38 (d, J= 7.5 Hz, 1H), 3.27-3.22 (m, 1H), 3.0 (dd, J_1= 7.8 Hz, J_2= 17.4 Hz, 1H), 2.79 (d, J= 15.3 Hz, 1H), 2.63 (d, J= 17.7 Hz, 1H), 2.31 (s, 3H), 2.0 (s, 3H), 1.80 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H), 1.58 (q, J= 7.2 Hz, 2H), 0.89 (t, J= 7.2 Hz, 3H), 0.76 (d, J= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{35}H_{43}N_5O_8$: 661.64. Found $(M+H)^+$: 662.3

Example 57



45

63

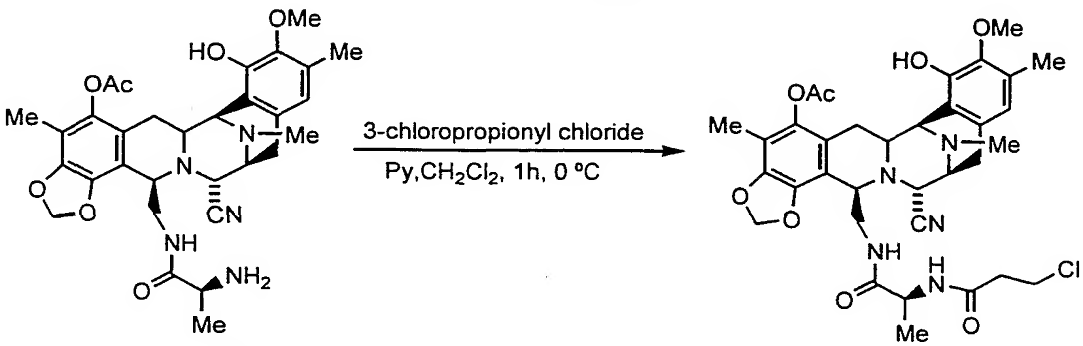
A solution of **43** (19 mg, 0.0364 mmol) in CH_2Cl_2 (0.3 ml), cinnamoyl chloride (6.06 mg , 0.0364 mmol) and pyridine (2.95 ml, 0.0364 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **63** (20.1 mg, 85%) as a white solid.

Rf: 0.65 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 6.42, (s, 1H), 6.01 (d, J= 1.5 Hz, 1H), 5.92 (d, J= 1.5 Hz, 1H), 5.73 (bs, 1H), 5.24 (t, J= 6.8 Hz, 1H), 4.12-4.08 (m, 3H), 3.66-3.64 (m, 2H), 3.58 (bs, 3H), 3.36 (d, J= 8.7 Hz, 1H), 3.29 (d, J= 12.0 Hz, 1H), 2.98 (dd, J_1= 8.1 Hz, J_2= 18 Hz, 1H), 2.33 (s, 6H), 2.29 (s, 3H), 2.01 (s, 3H), 1.84 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H).).

ESI-MS m/z: Calcd. for $C_{37}H_{38}N_4O_7$: 650.72. Found $(M+H)^+$: 651.2.

Example 58



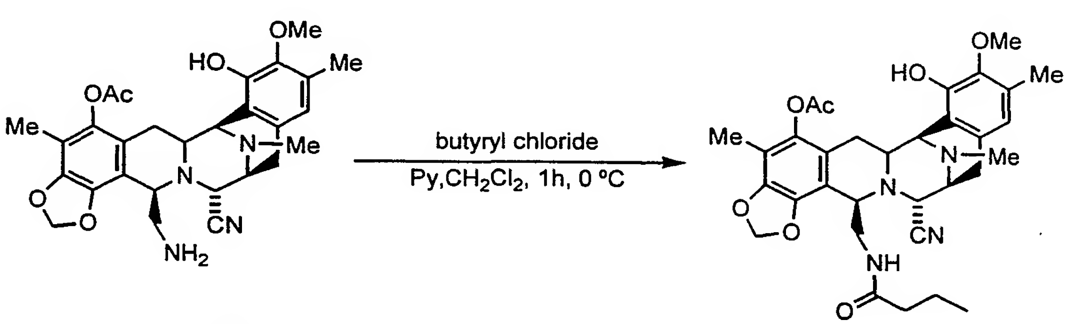
43 64

A solution of **43** (20 mg, 0.0338 mmol) in CH_2Cl_2 (0.3 ml), 3-chloropropionyl chloride (3.22 ml , 0.0338 mmol) and pyridine (2.73 ml, 0.0338 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **64** (20.5 mg, 89%) as a white solid.

Rf: 0.32 (EtOAc:Hexane 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) 6.48 (s, 3H), 6.28 (m, 1H), 5.99 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.86 (bs, 1H), 5.31 (m, 1H), 4.08-4.07 (m, 3H), 3.75 (s, 3H), 3.72-3.53 (m, 5H), 3.39 (d, J= 8.1 Hz, 1H), 3.24 (d, J= 12.0 Hz, 1H), 3.00 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.79 (d, J= 13.5 Hz, 1H), 2.50 (t, J= 6.3 Hz, 2H), 2.32 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.0 (s, 3H), 1.79 (dd, J_1= 12.3 Hz, J_2= 14.8 Hz, 1H), 0.81 (d, J= 6.3 Hz, 3H).

Example 59



45 65

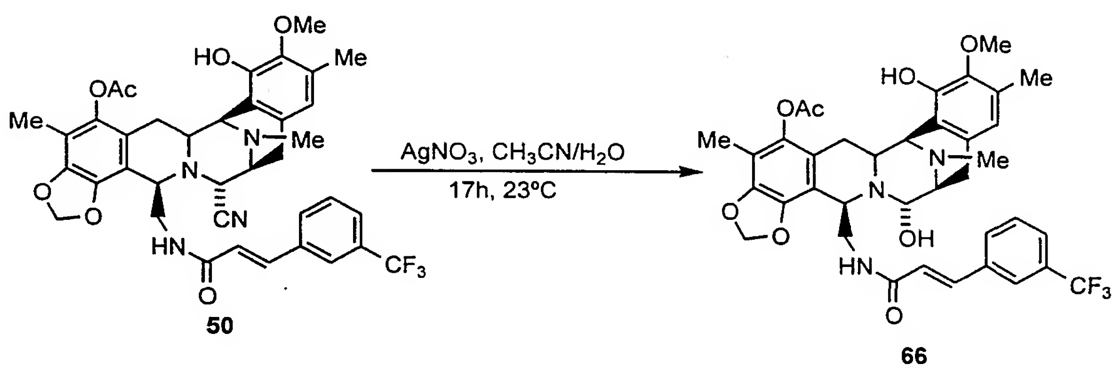
A solution of **43** (19 mg, 0.0364 mmol) in CH_2Cl_2 (0.3 ml), butyryl chloride (3.78 ml , 0.0364 mmol) and pyridine (2.95 ml, 0.0364 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 ml) and washed with 0.1 N HCl (5 ml). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 20:1) to afford **64** (19 mg, 87%) as a white solid.

Rf: 0.60 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) 6.50 (s, 1H), 5.98 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.75 (s,1H), 5.01 (t, J= 6.4 Hz, 1H), 4.10 –4.09 (m, 1H), 4.06 (d, J= 2.1 Hz, 1H), 4.03-4.02 (m, 1H), 3.76 (s, 3H), 3.67-3.60 (m, 1H), 3.42-3.35 (m, 2H), 3.29 (d, J= 12.0 Hz, 1H), 3.02 (dd, J_1= 7.8 Hz, J_2= 17.7 Hz, 1H), 2.79 (d, J= 14.1 Hz, 1H), 2.56 (d, J= 18.3 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.25 (s, 3H), 1.78 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H), 1.63 (s, 3H), 1.53-1.46 (m, 2H), 1.28-1.16 (m, 2H), 0.68 (t, J= 7.2 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{32}H_{38}N_4O_7$: 590.67. Found $(M+H)^+$: 591.2.

Example 60



To a solution of **50** (31.7 mg, 0.044 mmol) in CH_3CN/H_2O (1.5 ml/0.5 ml), $AgNO_3$ (225 mg, 1.32 mmol) was added and the reaction was stirred at 23°C for 17 h. Then brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was

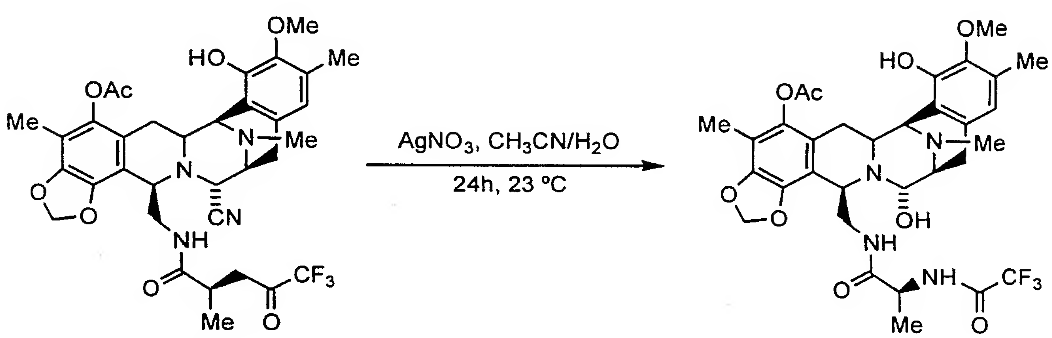
decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **66** (16 mg, 51%) as a white solid.

Rf: 0.26 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66-7.42 (m, 4H), 7.20 (bs, 1H), 6.44 (s, 1H), 5.97 (b, J= 1.2 Hz, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.76 (bs, 1H), 5.28 (bs, 1H), 4.54 (bs, 1H), 4.43 (bs, 1H), 4.00 (bs, 1H), 3.68-3.57 (m, 4H), 3.47 (d, J= 3.3 Hz, 1H), 3.40 (d, J= 11.7 Hz, 1H), 3.17 (d, J= 6.9 Hz, 1H), 2.92 (dd, J_1= 8.1 Hz, J_2= 17.7 Hz, 1H), 2.74 (d, J= 17.1 Hz, 1H), 2.48 (d, J= 18.6 Hz, 1H), 2.32 (s, 6H), 2.28 (s, 3H), 1.99 (s, 3H), 1.76 (dd, J_1= 12.0 Hz, J_2= 16.2 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{37}H_{38}F_3N_3O_8$: 709. Found (M^+-17): 692.3.

Example 61



53 67

To a solution of **53** (57 mg, 0.0828 mmol) in CH_3CN/H_2O (1.5 mL/0.5 ml), $AgNO_3$ (650 mg, 3.81 mmol) was added and the reaction was stirred at 23°C for 24 h. Then, brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **67** (28 mg, 50%) as a white solid.

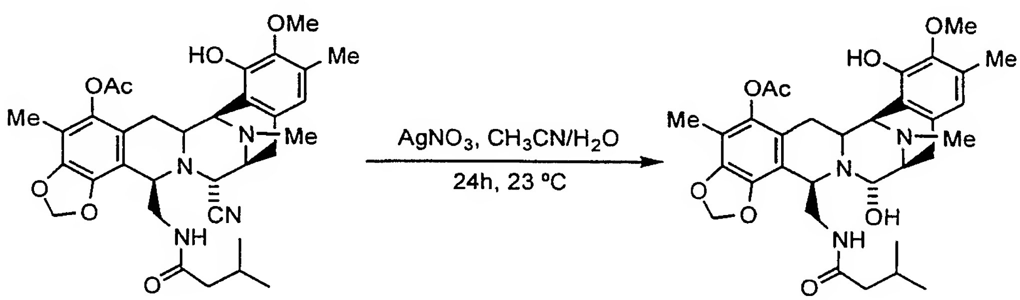
Rf: 0.28 (EtOAc:MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) d

6.47 (s, 1H), 5.97 (s, 1H), 5.88 (s, 1H), 5.35 (bs, 1H), 4.51 (bs, 1H), 4.41 (bs, 1H), 4.12-4.05 (m, 1H), 4.00 (d, *J*= 2.7 Hz, 1H), 3.77 (s, 3H), 3.64 (bs, 1H), 3.46 (d, *J*= 3.3 Hz, 1H), 3.34 (d, *J*= 11.4 Hz, 1H), 3.18 (d, *J*= 7.5 Hz, 1H), 2.95 (dd, J_1= 8.4 Hz, J_2= 18.3 Hz, 1H), 2.70 (d, *J*= 15.6 Hz, 1H), 2.48 (d, *J*= 17.7 Hz, 1H), 2.28 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H), 1.98 (s, 3H), 1.68 (dd, J_1= 12 Hz, J_2= 15.6 Hz, 1H), 0.86 (d, *J*= 6.3 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{32}H_{37}F_3N_4O_9$: 678.66. Found (M^+-17): 661.2.

Example 62



48 **68**

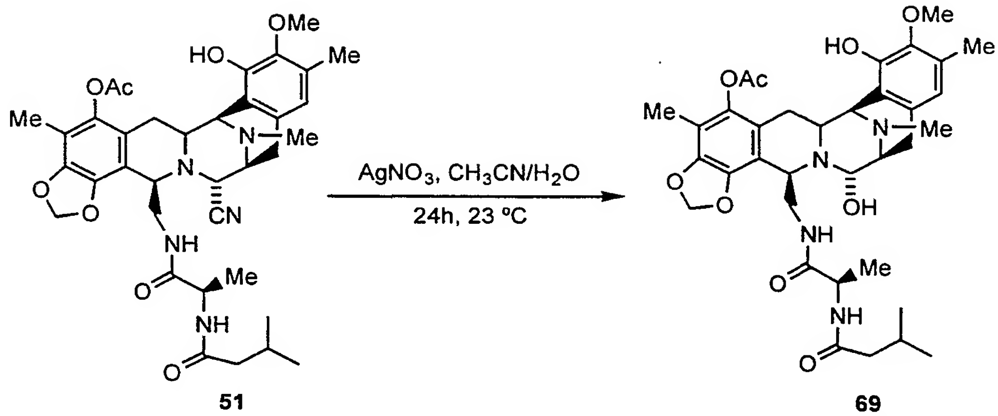
To a solution of **48** (32 mg, 0.0529 mmol) in CH_3CN/H_2O (1.5 ml/0.5 ml), $AgNO_3$ (270 mg, 1.58 mmol) was added and the reaction was stirred at 23°C for 24 h. Then, brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **68** (18 mg, 56%) as a white solid.

Rf: 0.40 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) d 6.50 (s, 1H), 5.95 (d, *J*= 1.2 Hz, 1H), 5.88 (d, *J*= 1.2 Hz, 1H), 5.23 (d, *J*= 6.9 Hz, 1H), 4.45 (d, *J*= 3.3 Hz, 1H), 4.38 (s, 1H), 4.01 (d, *J*= 2.4 Hz, 1H), 3.78 (m, 1H), 3.77 (s, 3H), 3.41-3.37 (m, 1H), 3.17-3.15 (m, 1H), 2.96 (dd, J_1= 7.8 Hz, J_2= 18.0 Hz, 1H), 2.70 (d, *J*= 15.3 Hz, 1H), 2.40 (d, *J*= 18.0 Hz, 1H), 2.30 (s, 6H), 2.27 (s, 3H), 1.76-1.65 (m, 1H), 1.35-1.25 (m, 2H), 0.89-0.82 (m, 1H), 0.69 (d, *J*= 6.6 Hz, 3H), 0.58 (d, *J*= 6.6

Hz, 3H)

Example 63

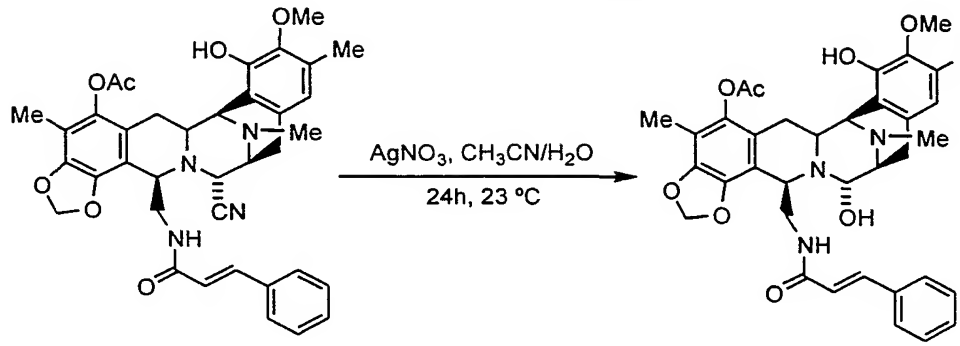


To a solution of **51** (27 mg, 0.04 mmol) in CH_3CN/H_2O (1.5 ml/0.5 ml), $AgNO_3$ (204 mg, 1.19 mmol) was added and the reaction was stirred at 23°C for 24 h. Then, brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **69** (10 mg, 38%) as a white solid.

Rf: 0.38 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) d 6.48 s, 1H), 6.16 (bs, 1H), 5.98 (d, J= 1.5 Hz, 1H), 5.89 (d, J= 1.5 Hz, 1H), 5.33 (t, J= 6.0 Hz, 1H), 4.50 (m, 1H), 4.40 (m, 1H), 4.11-4.09 (m, 1H), 4.00 (d, J= 2.6Hz, 1H), 3.78 (s, 3H), 3.41-3.32 (m, 3H), 3.18 (d, J= 8.4 Hz, 1H), 2.94 (dd, J_1= 8.4 Hz, J_2= 18.3 Hz, 1H), 2.70 (d, J= 14.4 Hz, 1H), 4.45 (d, J= 18.3 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.04 (s, 3H), 2.00-1.86 (m, 3H), 1.73 (m, 1H), 0.87 (d, J= 6.3 Hz, 6H).

Example 64



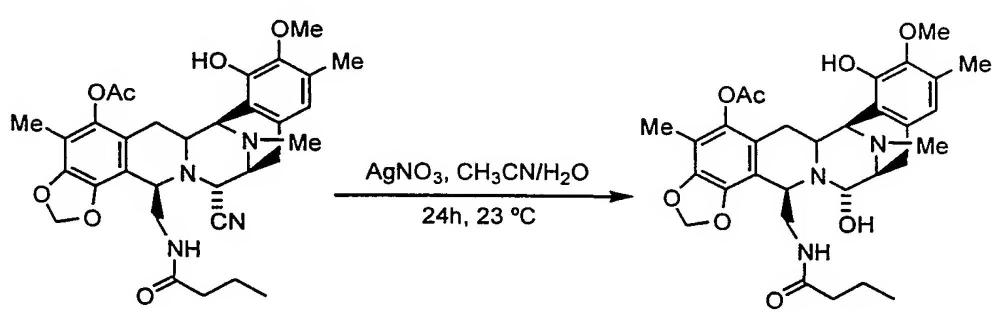
63 70

To a solution of **63** (15 mg, 0.023 mmol) in CH_3CN/H_2O (1.5 ml/0.5 ml), $AgNO_3$ (118 mg, 0.691 mmol) was added and the reaction was stirred at 23°C for 24 h. Then, brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **70** (20.1 mg, 85%) as a white solid.

Rf: 0.43 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) d 7.38-7.28 (m, 5H), 6.48 (s, 1H), 5.98 (d, J=1.5 Hz, 1H), 5.91 (d, J=1.5 Hz, 1H), 5.75 (bs, 1H), 5.38 (brd, 1H), 5.30 (bs, 1H), 4.53 (m, 1H), 4.42 (m, 1H), 4.02 (d, J=2.7 Hz, 1H), 3.78-3.65 (m, 5H), 3.46-3.40 (m, 2H), 3.17 (d, J=7.8 Hz, 1H), 2.94 (dd, J_1=7.8 Hz, J_2=17.7 Hz, 1H), 2.73 (d, J=16.8 Hz, 1H), 2.45 (d, J=18.0 Hz, 1H), 2.31 (s, 6H), 2.28 (s, 3H), 1.97 (s, 3H), 1.77 (dd, J_1=12.0 Hz, J_2=15.3 Hz, 1H).

Example 65

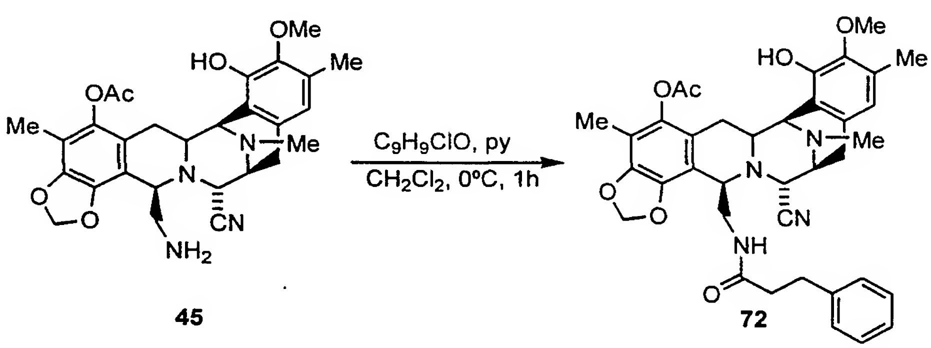


65 71

To a solution of **65** (25 mg, 0.042 mmol) in CH_3CN/H_2O (1.5 ml/0.5 ml), $AgNO_3$ (215.56 mg, 1.269 mmol) was added and the reaction was stirred at 23°C for 24 h. Then, brine (10 ml) and Aq sat $NaHCO_3$ (10 ml) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 ml). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:2) to afford **71** (16mg, 65%) as a white solid.

Rf: 0.0.5 (EtOAc:MeOH 5:2).
^{1}H NMR (300 MHz, $CDCl_3$) d 6.50 (s, 1H), 5.95 (d, J=1.5 Hz, 1H), 5.78 (s, 1H), 5.19 (bs, 1H), 4.45 (d, J=3.3 Hz, 1H), 4.37 (bs, 1H), 4.11 (brd, J=4.8 Hz, 1H), 4.01 (d, J=2.1 Hz, 1H), 3.76 (s, 1H), 3.71-3.69 (m, 1H), 3.49-3.35 (m, 1H), 3.24 (d, J=13.5 Hz, 1H), 3.15 (d, J=9.3 Hz, 1H), 2.95 (dd, J_1=8.1 Hz, J_2=17.7 Hz, 1H), 2.70 (d, J=15.6 Hz, 1H), 2.40 (d, J=18.0 Hz, 1H), 2.31 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 1.96 (s, 3H), 1.75-1.66 (m, 1H), 1.52-1.17 (m, 2H), 0.66 (t, J=7.2 Hz, 3H).

Example 66



To a solution of **45** (35 mg, 0.0672 mmol) in CH_2Cl_2 (0.3 mL), hydrocinnamoyl chloride (11.58 µl, 0.0672 mmol) and pyridine (5.43 µL, 0.0672 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered,

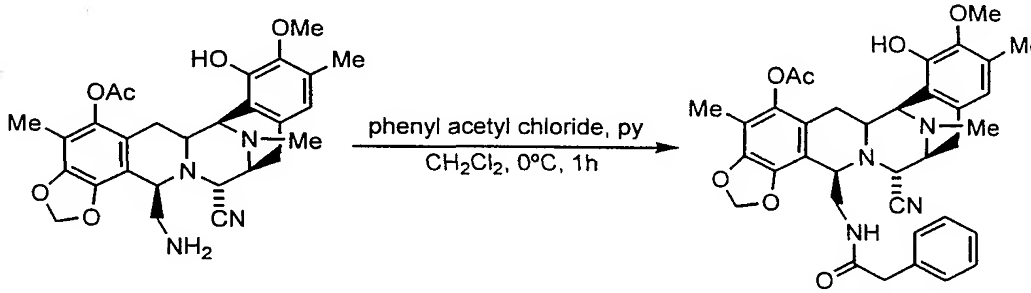
and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex: ethyl acetate 2:1 to ethyl acetate) to afford **72** (30 mg, 68%) as a white solid.

Rf: 0.51 (ethyl acetate:MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.12 (m, 3H), 7.05-7.00 (m, 2H), 5.97 (d, *J*= 1.2 Hz, 1H), 5.91 (d, *J*= 1.2 Hz, 1H), 5.73 (s, 1H), 5.04 (brt, 1H), 4.08 (d, *J*= 2.4 Hz, 1H), 4.02 (bs, 1H), 4.00 (d, *J*= 2.4 Hz, 1H), 3.58 (dd, J_1= 4.5 Hz, J_2= 13.8 Hz, 1H), 3.47 (bs, 3H), 3.33 (d, *J*= 7.5 Hz, 1H), 3.29 (dt, J_1= 2.7 Hz, J_2= 11.7 Hz, 1H), 3.00 (dd, J_1= 7.8 Hz, J_2= 18.3 Hz, 1H), 2.79 (d, *J*= 14.1 Hz, 1H), 2.58-2.50 (m, 3H), 2.32 (s, 3H), 2.29 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.94-1.76 (m, 4H).

ESI-MS m/z: Calcd. for $C_{37}H_{40}N_4O_7$: 652.7. Found $(M+Na)^+$: 675.3.

Example 67



45 73

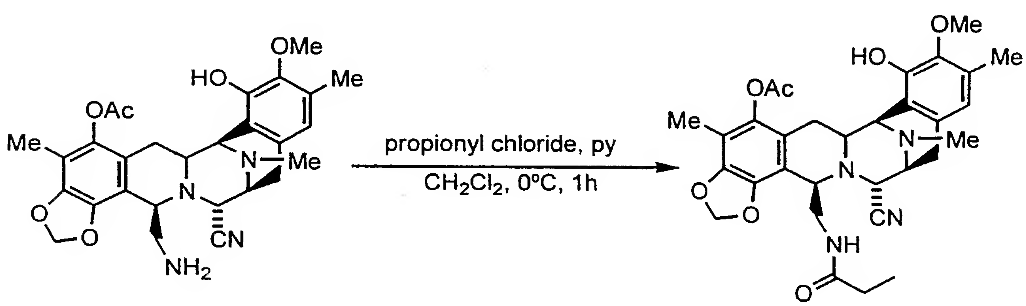
To a solution of **45** (45 mg, 0.0576 mmol) in CH_2Cl_2 (0.3 mL), phenyl acetyl chloride (7.61 μl, 0.0576 mmol) and pyridine (4.6 μL, 0.0576 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 3:1 to Hex:ethyl acetate 1:1) to afford **73** (25.8 mg, 70 %) as a white solid.

Rf: 0.5 (Hex:ethyl acetate:MeOH 5:10:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18-7.17 (m, 3H), 6.85 (bs, 2H), 6.54 (s, 1H), 5.89 (d, J= 1.5Hz, 1H), 5.83 (d, J= 1.5 Hz, 1H), 5.76 (s, 1H), 5.08 (bs, 1H), 4.12 (d, J= 2.1 Hz, 1H), 4.09 (d, J= 2.1 Hz, 1H), 3.98 (bs, 1H), 3.73 (s, 3H), 3.51-3.46 (m, 2H), 3.35 (d, J= 8.4 Hz, 1H), 3.25 (dt, J_1= 2.7 Hz, J_2= 12.0 Hz, 1H), 3.03 (d, J= 8.7 Hz, 1H), 3.02-2.94 (m, 2H), 2.75 (d, J= 16.8 Hz, 1H), 2.63 (d, J= 18.0 Hz, 1H), 2.35 (s, 3H), 2.30 (s, 3H), 2.22 (s. 3H9, 1.98 (s, 3H), 1.80 (dd, J_1= 12.0 Hz, J_2= 16.2 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{36}H_{38}N_4O_7$: 638.7. Found $(M+1)^+$: 639.2.

Example 68



45 74

To a solution of **45** (30 mg, 0.0576 mmol) in CH_2Cl_2 (0.3 mL), propyonyl chloride (5 μL, 0.0576 mmol) and pyridine (4.6 μL, 0.0576 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 5:1 to Hex:ethyl acetate 1:1 to ethyl acetate) to afford **74** (23 mg, 70 %) as a white solid.

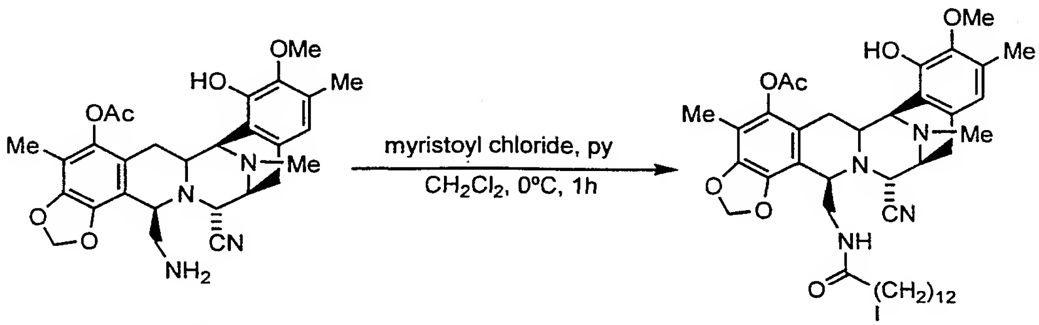
Rf: 0.59 ((Hex:ethyl acetate:MeOH 5:10:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s,1H), 5.97 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.76 (s, 1H), 5.00 (t, 1H), 4.09 (d, J= 1.2 Hz, 1H), 4.04 (bs, 2H), 3.74 (s, 3H), 3.62 (dd, J_1= 6.6 Hz, J_2= 13.2 Hz, 1H), 3.43 (bs, 1H), 3.37 (d, J= 8.4 Hz, 1H), 3.29 (d, J= 12.0 Hz, 1H), 3.02 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.80 (d, J= 14.4 Hz, 1H), 2.55 (d, J= 18.0 Hz, 1H),

2.31 (s, 3H), 2.24 (s, 3H), 2.00 (s, 3H), 1.78 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H), 1.64-1.50 (m, 2H), 0.70 (t, J= 7.8 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{31}H_{36}N_4O_7$: 576.6. Found $(M+1)^+$: 577.2.

Example 69



45 75

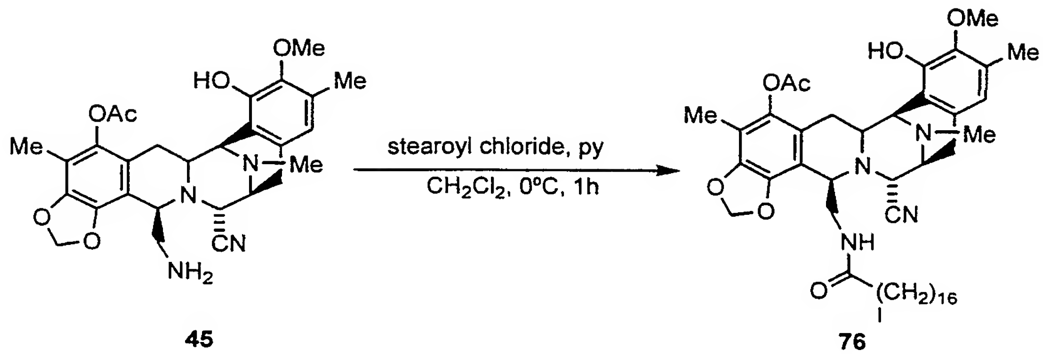
To a solution of **45** (15 mg, 0.0288 mmol) in CH_2Cl_2 (0.25 mL), myristoyl chloride (7.83 µL, 0.0288 mmol) and pyridine (2.3 µL, 0.0288 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 6:1 to Hex:ethyl acetate 1:1) to afford **75** (15 mg, 71 %) as a white solid.

Rf: 0.65 (Hex:ethy acetate:MeOH 10:10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 5.97 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.72 (s, 1H), 4.99 (t, 1H), 4.09 (d, J= 1.5 Hz, 1H), 4.05 (d, J= 1.5 Hz, 1H), 4.02 (bs, 1H), 3.76 (s, 3H), 3.61-3.59 (m, 1H), 3.39 (bs, 1H), 3.35 (d, J= 7.8 Hz, 1H), 3.29 (d, J= 12.3 Hz, 1H), 3.04 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 15.6 Hz, 1H), 2.55 (d, J= 18.3 Hz, 1H), 2.32 (s, 6H), 2.25 (s, 3H), 1.99 (s, 3H), 1.78 (dd, J_1= 12.3 Hz, J_2= 15.0 Hz, 1H), 1.25-1.24 (m, 12H), 0.87 (d, J= 6.0 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{42}H_{58}N_4O_7$: 730.9. Found $(M+1)^+$: 731.4.

Example 70



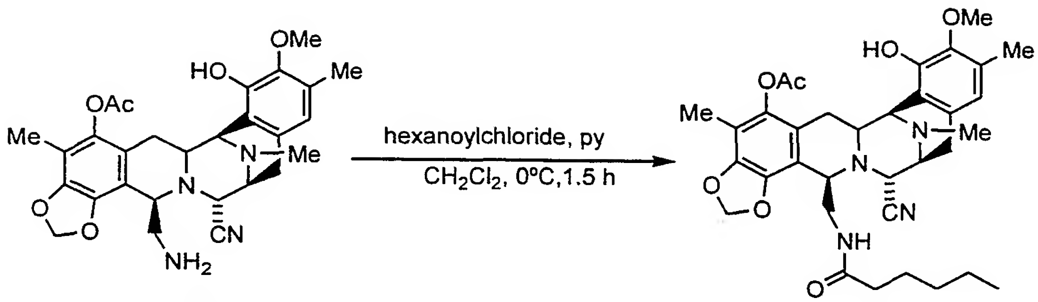
To a solution of **45** (15 mg, 0.0288 mmol) in CH_2Cl_2 (0.25 mL), stearoyl chloride (9.7 μL, 0.0288 mmol) and pyridine (2.3 μL, 0.0288 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 3:1 to Hex:ethyl acetate 1:1) to afford **76** (16 mg, 70 %) as a white solid.

Rf: 0.46 (Hex:ethyl acetate:MeOH 10:10:1).

^{1}H NMR NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 5.98 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.73 (s, 1H), 4.99 (t, J= 5.7 Hz, 1H), 4.09 (d, J= 1.8 Hz, 1H), 4.05 (d, J= 2.4 Hz, 1H), 4.01 (bs, 1H), 3.76 (s, 3H), 3.61-3.59 (m, 1H), 3.38 (bs, 1H), 3.36 (d, J= 7.2 Hz, 1H), 3.28 (d, J= 12.0 Hz, 1H), 3.03 (dd, J_1= 7.8 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 15.9 Hz, 1H), 2.57 (d, J= 18.3 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H), 1.99 (s, 3H), 1.77 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H), 1.25-1.24 (m, 16H), 0.87 (d, J= 6.3 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{46}H_{66}N_4O_7$: 786.4. Found $(M+22)^+$: 809.5.

Example 71



45 **77**

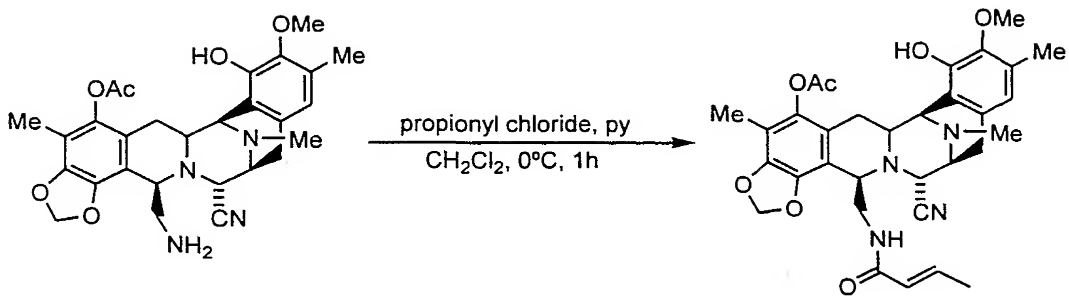
To a solution of **45** (31 mg, 0.0595 mmol) in CH_2Cl_2 (0.3 mL), hexanoyl chloride (8.32 μL, 0.0595 mmol) and pyridine (4.8 μL, 0.0595 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 3:2 to ethyl acetate) to afford **77** (26 mg, 70 %) as a white solid.

Rf: 0.65 (ethyl acetate MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.98 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.74 (s, 1H), 5.00 (t, J= 5.4 Hz, 1H), 4.09 (d, J= 2.7 Hz, 1H), 4.05 (d, J= 2.4 Hz, 1H), 4.01 (bs, 1H), 3.76 (s, 3H), 3.61-3.58 (m, 1H), 3.02 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 14.4 Hz, 1H), 2.56 (d, J= 18.3 Hz, 1H), 2.31 (s, 6H), 2.25 (s, 3H), 2.00 (s, 3H), 1.78 (dd, J_1= 12.0 Hz, J_2= 15.9 Hz, 1H), 1.53-1.40 (m, 2H), 1.29-1.12 (m, 4H), 1.07-0.97 (m, 2H), 0.81 (t, J= 7.5 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{34}H_{42}N_4O_7$: 618.7. Found $(M+1)^+$: 619.3.

Example 72



45

78

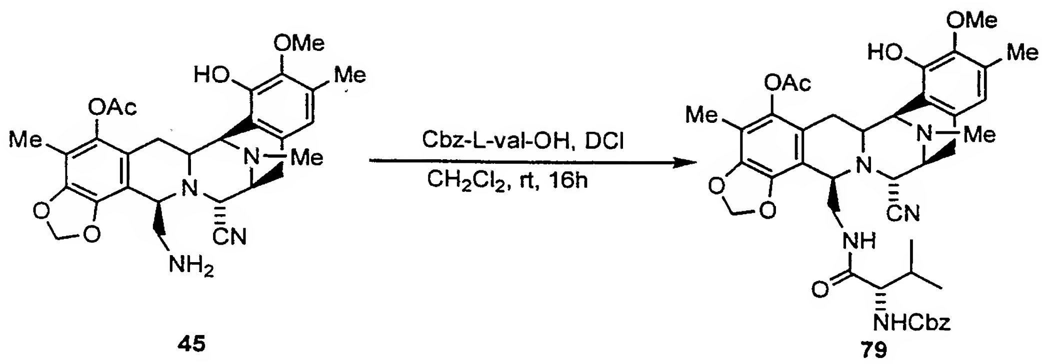
To a solution of **45** (20 mg, 0.0384 mmol) in CH_2Cl_2 (0.3 mL), trans-crotonyl chloride (3.68 μL, 0.0384 mmol) and pyridine (3.1 μL, 0.0384 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:ethyl acetate 4:1 to ethyl acetate) to afford **78** (16 mg, 71 %) as a white solid.

Rf: 0.55 (ethyl acetate:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50-6.40 (m, 1H), 6.46 (s, 1H), 5.97 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.77 (s, 1H), 5.08 (bst, 1H), 4.10 (d, J= 1.5 Hz, 1H), 4.05 (m, 2H), 3.78 (s, 3H), 3.67 (bs, 1H), 3.42-3.29 (m, 3H), 3.04 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 15.3 Hz, 1H), 2.53 (d, J= 18.3 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 1.98 (s, 3H), 1.79 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H), 1.70 (dd, J_1= 1.2 Hz, J_2= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{32}H_{36}N_4O_7$: 588.6. Found $(M+1)^+$: 589.3.

Example 73



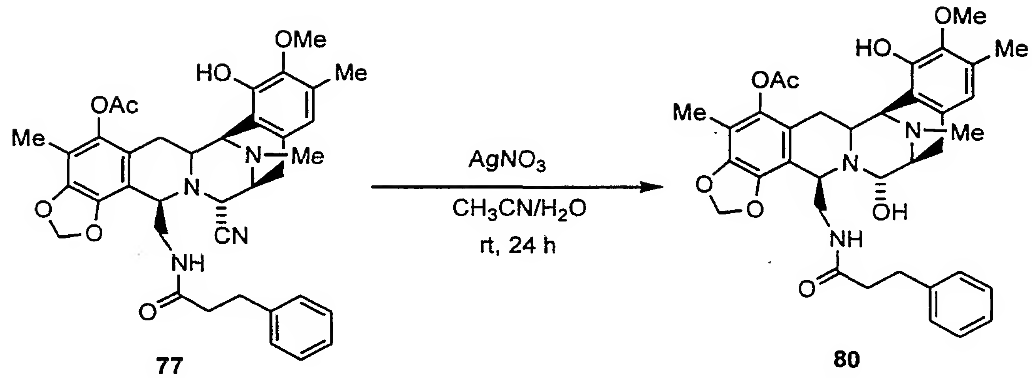
To a solution of **45** (50 mg, 0.096 mmol) in CH_2Cl_2 (0.5 mL), Cbz-L-Val-OH (24.12 mg, 0.096 mmol) and carbonyl diimidazole (18.7 mg, 0.115 mmol) were added at 0 °C. The reaction mixture was stirred for 16 h at room temperature and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 4:1) to afford **79** (25 mg, 34 %) as a white solid.

Rf: 0.7 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 5H), 6.45 (s, 1H), 5.96 (s, 1H), 5.90 (bs, 1H), 5.82 (s, 1H), 5.53 (bs, 1H), 5.09 (bs, 1H), 5.05 (d, J= 3.3 Hz, 2H), 4.16 (bs, 1H), 4.09 (d, J= 2.4 Hz, 1H), 4.02 (bs, 1H), 3.75 (s, 3H), 3.74 (m, 1H), 3.37-3.35 (m, 2H), 3.26-3.21 (m, 3H), 3.00 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.77 (d, J= 15.6 Hz, 1H), 2.55 (d, J= 18.0 Hz, 1H), 2.30 (s, 3H), 2.27 (s, 3H), 2.25 (s, 3H), 1.98 (s, 3H), 1.70-1.66 (m, 1H), 0.65 (d, J= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{41}H_{47}N_5O_9$: 753.8. Found $(M+1)^+$: 754.2.

Example 74



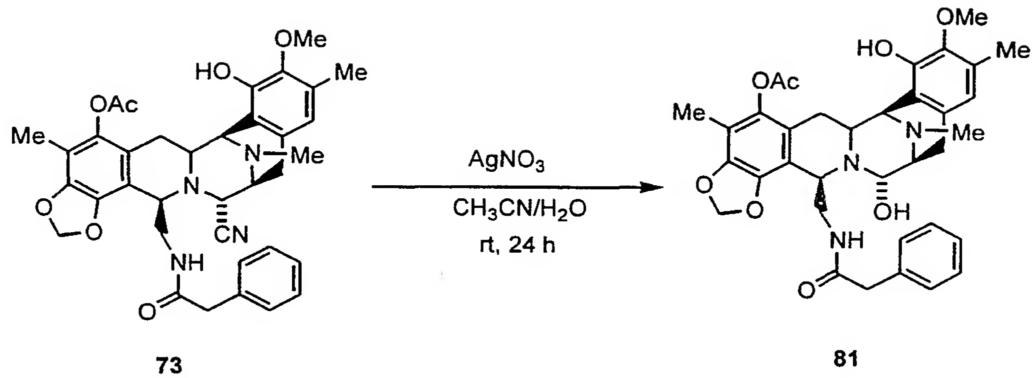
To a solution of **72** (18 mg, 0.0275 mmol) in CH_3CN/H_2O (1.5 mL/0.5 mL), $AgNO_3$ (140.5 mg, 0.827 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 10:1) to afford **80** (13 mg, 74 %) as a white solid.

Rf: 0.37 (EtOAc:MeOH 5:1).

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.23-7.11 (m, 3H), 7.06-7.01 (m, 2H), 6.43 (s, 1H), 5.95 (d, *J*= 1.2 Hz, 1H), 5.88 (d, *J*= 1.2 Hz, 1H), 5.71 (bs, 1H), 5.19 (bs, 1H), 4.45 (d, *J*= 3.0 Hz, 1H), 4.37 (bs, 1H), 4.02-3.96 (m, 1H), 3.75-3.68 (m, 2H), 3.48 (s, 3H), 3.41-3.36 (m, 2H), 3.28-3.24 (m, 1H), 3.15 (d, *J*= 7.5 Hz, 1H), 3.01-2.88 (m, 2H), 2.70 (d, *J*= 15.9 Hz, 1H), 2.57-2.51 (m, 2H), 2.31 (s, 3H), 2.27 (s, 3H), 2.00 (s, 6H), 1.77-1.68 (m, 1H).

ESI-MS m/z: Calcd. for $C_{36}H_{41}N_3O_8$: 643.3. Found $(M-17)^+$: 626.2.

Example 75



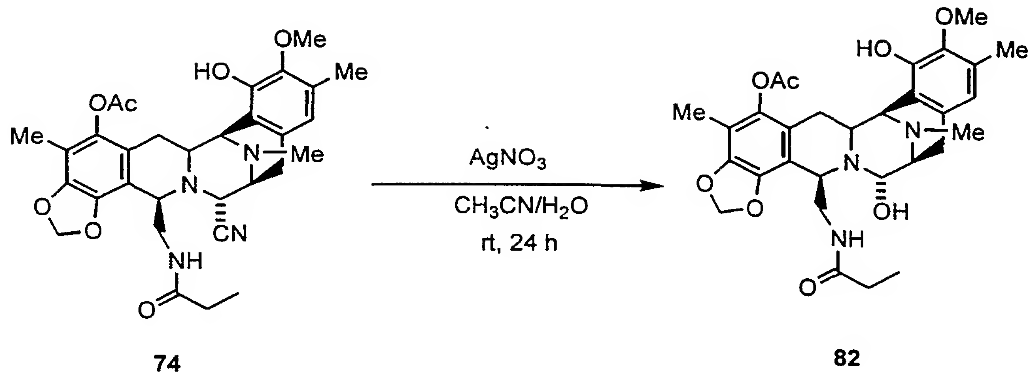
To a solution of **73** (23 mg, 0.036 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (183 mg, 1.08 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc:MeOH 5:1 to MeOH) to afford **81** (9.3 mg, 41 %) as a white solid.

Rf: 0.3 (EtOAc:MeOH 5:1).

^{1}HNMR (300 MHz, $CDCl_3$) δ 7.17-7.13 (m, 3H), 6.85 (m, 2H), 6.54 (s, 1H), 5.90 (d, *J*= 1.5 Hz, 1H), 5.84 (d, *J*= 1.5 Hz, 1H), 5.22 (m, 1H), 4.43 (bs, 1H), 4.39 (d, *J*= 2.4 Hz, 1H), 4.00 (d, *J*= 2.4 Hz, 1H), 3.71 (s, 3H), 3.64-3.29 (m, 2H), 3.16 (d, *J*= 8.7 Hz, 1H), 2.98-2.88 (m, 3H), 2.67 (d, *J*= 14.8 Hz, 1H), 2.45 (d, *J*= 18.3 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 1.97 (s, 3H), 1.68 (dd, J_1= 12.8 Hz, J_2= 14.7 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{35}H_{39}N_3O_8$: 629.7. Found (M^+- OH): 612.3.

Example 76



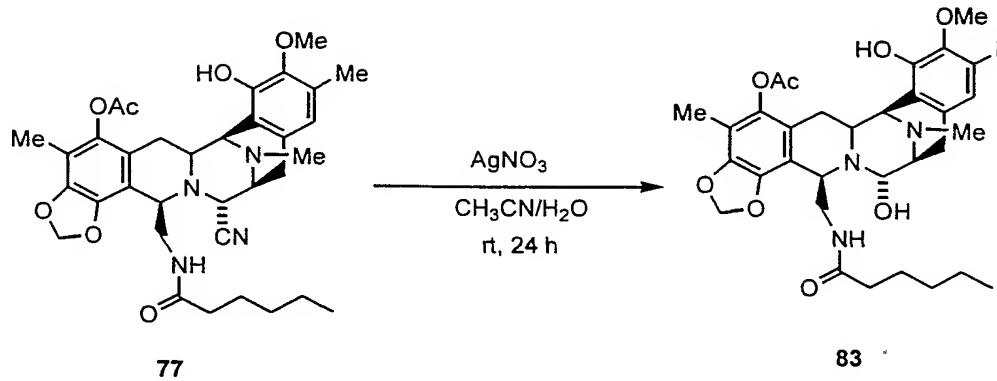
To a solution of **74** (20 mg, 0.0346 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (176.6 mg, 1.04 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 1:1) to afford **82** (12.9 mg, 66 %) as a white solid.

Rf: 0.3 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.95 (d, J= 1.2 Hz, 1H), 5.89 (d, J= 1.2 Hz, 1H), 5.19 (d, 1H), 4.46 (d, J= 3.0 Hz, 1H), 4.38 (d, J= 1.8 Hz, 1H), 4.00 (d, J= 2.1 Hz, 1H), 3.74 (s, 3H), 3.70-3.66 (m, 1H), 3.38 (dt, J_1= 2.7 Hz, J_2= 13.2 Hz, 1H), 3.25 (d, J= 13.8 Hz, 1H), 3.16 (d, J= 7.5 Hz, 1H), 2.96 (dd, J_1= 7.2 Hz, J_2= 17.7 Hz, 1H), 2.71 (d, J= 15.6 Hz, 1H), 2.40 (d, J= 18.0 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H), 1.97 (s, 3H), 1.71 (dd, J_1= 11.7 Hz, J_2= 15.3 Hz, 1H), 1.60-1.48 (m, 2H), 0.67 (t, J= 7.5 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{30}H_{37}N_3O_8$: 567.6. Found $(M- 17)^+$: 550.2.

Example 77



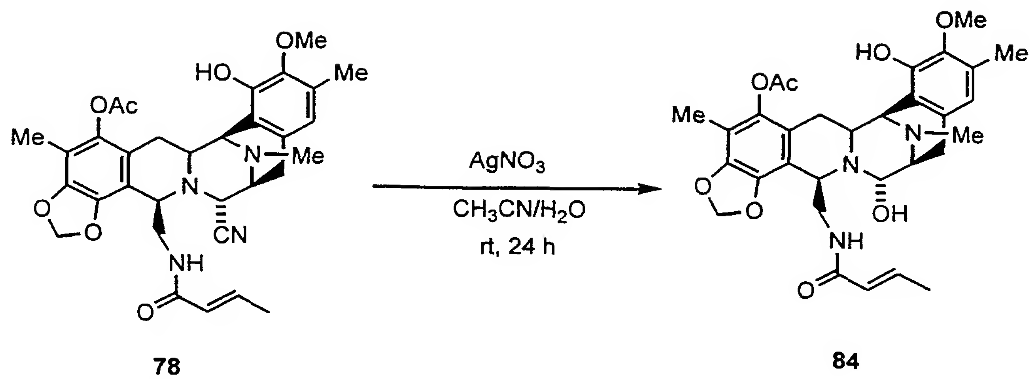
To a solution of **77** (14 mg, 0.0226 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (115.3 mg, 0.68 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **83** (9 mg, 65 %) as a white solid.

Rf: 0.25 (EtOAc:MeOH 5:1).

^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.96 (d, *J*= 1.5 Hz, 1H), 5.89 (d, *J*= 1.5 Hz, 1H), 5.73 (bs, 1H), 4.44 (d, *J*= 3.6 Hz, 1H), 4.37 (s, 1H), 4.01 (d, *J*= 2.4 Hz, 1H), 3.77 (s, 3H), 3.73-3.64 (m, 1H), 3.39 (dt, J_1= 3.0 Hz, J_2= 9.3 Hz, 1H), 3.22 (d, *J*= 14.5 Hz, 1H), 3.16 (d, *J*= 7.5 Hz, 1H), 2.95 (dd, J_1= 8.1 Hz, J_2= 17.4 Hz, 1H), 2.70 (d, *J*= 14.5 Hz, 1H), 2.41 (d, *J*= 18.3 Hz, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.25 (s, 3H), 1.96 (s, 3H), 1.71 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H), 1.48-1.46 (m, 2H), 1.24-1.10 (m, 4H), 1.00-0.95 (m, 2H), 0.80 (t, *J*= 7.2 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{33}H_{43}N_3O_8$: 609.7. Found $(M-17)^+$: 592.3.

Example 78



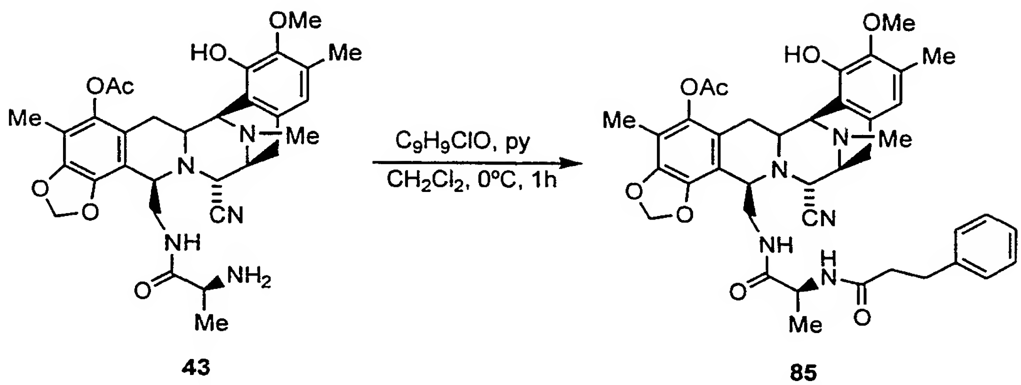
To a solution of **78** (15 mg, 0.025 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (130 mg, 0.764 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 1:1) to afford **84** (10 mg, 71 %) as a white solid.

Rf: 0.19 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.47-6.37 (m, 1H), 5.94 (d, J= 1.5 Hz, 1H), 5.88 (d, J= 1.5 Hz, 1H), 5.77 (bs, 1H), 5.26 (d, J= 5.7 Hz, 1H), 4.93 (d, J= 14.7 Hz, 1H), 4.48 (d, J= 11.1 Hz, 1H), 4.38 (d, J= 2.7 Hz, 1H), 4.02 ((d, J= 2.1 Hz, 1H), 3.79 (s, 3H), 3.76-3.72 (m, 1H), 3.42 (dt, J_1= 2.7 Hz, J_2= 12.0 Hz, 1H), 3.28 (d, J= 13.2 Hz, 1H), 3.15 (d, J= 6.6 Hz, 1H), 2.96 (dd, J_1= 8.7 Hz, J_2= 18.0 Hz, 1H), 2.70 (d, J= 15.0 Hz, 1H), 2.38 (d, J= 18.0 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 1.95 (s, 3H), 1.72 (dd, J_1= 12.3 Hz, J_2= 17.4 Hz, 1H), 1.98 (dd, J_1= 1.5 Hz, J_2= 6.9 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{31}H_{37}N_3O_8$: 579.6. Found $(M-17)^+$: 562.3.

Example 79



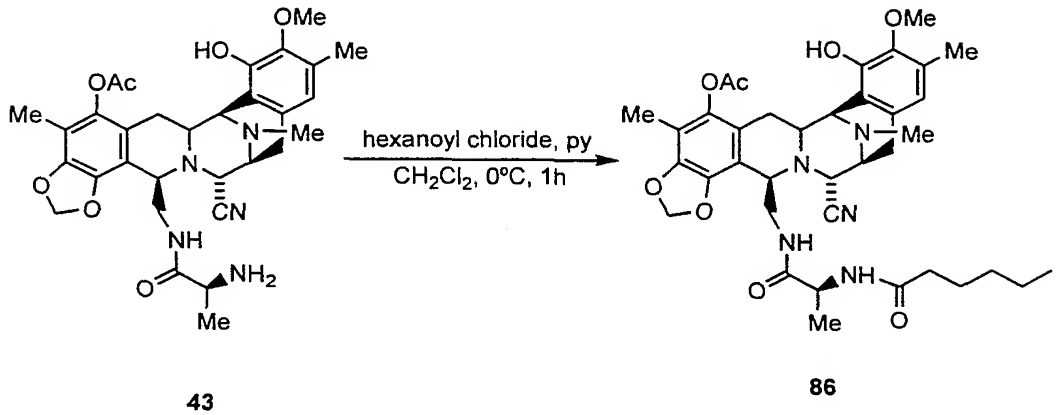
To a solution of **43** (25 mg, 0.422 mmol) in CH_2Cl_2 (0.3 mL), hydrocinnamoyl chloride (6.27 μL, 0.422 mmol) and pyridine (3.41 μL, 0.422 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex: EtOAc 4:1 to EtOAc) to afford **85** (30 mg, 68 %) as a white solid.

Rf: 0.54 (EtOAcMeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H), 6.45 (s, 1H), 6.07 (brd, 1H), 5.99 (d, J= 1.2 Hz, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.88 (s, 1H), 5.31 (brt, 1H), 4.09-4.06 (m, 3H), 3.80-3.75 (m, 1H), 3.73 (s, 3H), 3.57-3.51 (m, 2H), 3.38 (d, J= 7.5 Hz, 1H), 3.24 (m, 1H), 3.00 (dd, J_1= 8.4 Hz, J_2= 18.0 Hz, 1H), 2.89-2.85 (m, 2H), 2.79 (d, J= 16.5 Hz, 1H), 2.61 (d, J= 18.0 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.00 (s, 3H), 1.79 (dd, J_1= 12.3 Hz, J_2= 16.2 Hz, 1H), 0.72 (d, J= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{40}H_{45}N_5O_8$: 723.8. Found $(M+23)^+$: 746.3.

Example 80



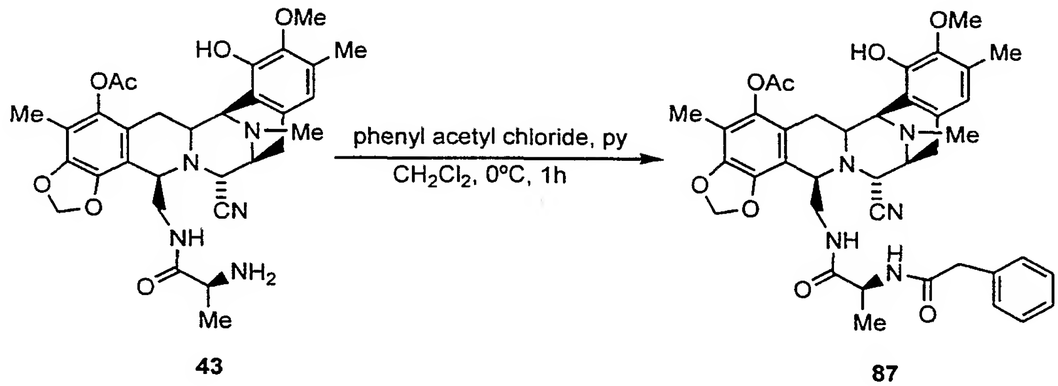
To a solution of **43** (20 mg, 0.0338 mmol) in CH_2Cl_2 (0.25 mL), hexanoyl chloride (4.72 μL, 0.0338 mmol) and pyridine (2.73 μL, 0.0338 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 1:1 to EtOAc) to afford **86** (10 mg, 43 %) as a white solid.

Rf: 0.74 (EtOAc:MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.47 (s, 1H), 6.12 (brd, 1H), 6.00 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.30 (m, 1H), 4.09-3.99 (m, 3H), 3.84-3.82 (m, 1H), 3.75 (s, 3H), 3.57-3.55 (m, 2H), 3.39 (d, J= 6.9 Hz, 1H), 3.24 (d, J= 12.0 Hz, 1H), 3.04 (dd, J_1= 9.0 Hz, J_2= 18.3 Hz, 1H), 2.77 (d, J= 115.3Hz, 1H), 2.63 (d, J= 18.0 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.25 (s, 3H), 2.00 (s, 3H), 1.80 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H), 1.55-1.50 (m, 2H), 1.30-1.22 (m, 6H), 0.87 (t, J= 6.9 Hz, 3H), 0.75 (d, J= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{37}H_{47}N_5O_8$: 689.8. Found $(M+1)^+$: 690.3.

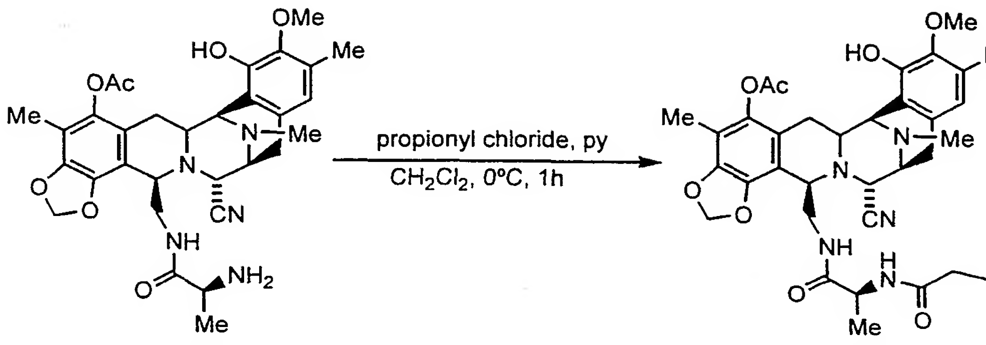
Example 81



To a solution of **43** (33 mg, 0.0557 mmol) in CH_2Cl_2 (0.4 mL), phenyl acetyl chloride (7.36 μL, 0.0557 mmol) and pyridine (4.5 μL, 0.0557 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 2:1) to afford **87** (13 mg, 32 %) as a white solid.

Rf: 0.63 (Hex:EtOAc:MeOH 5:10:2).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.20 (m, 5H), 6.26 (s, 1H), 6.14 (d, J= 6.6 Hz, 1H), 5.98 (d, J= 1.2 Hz, 1H), 5.83 (s, 1H), 5.27 (t, J= 6.2 Hz, 1H), 4.11 (d, J= 2.1 Hz, 1H), 4.07 (d, J= 3.0 Hz, 1H), 4.04 (s, 1H), 3.86-3.81 (m, 1H), 3.70 (s, 3H), 3.54-3.53 (m, 2H), 3.44 (bs, 2H), 3.36 (d, J= 8.1 Hz, 1H), 3.22 (dt, J_1= 2.7 Hz, J_2= 12.0 Hz, 1H), 2.93 (dd, J_1= 7.2 Hz, J_2= 18.3 Hz, 1H), 2.77 (d, J= 14.4 Hz, 1H), 2.59 (d, J= 18.0 Hz, 1H), 2.31 (s, 3H), 2.26 (s, 3H), 2.17 (s, 3H), 2.01 (s, 3H), 1.78 (dd, J_1= 10.8 Hz, J_2= 15.6 Hz, 1H), 0.65 (d, J= 6.3 Hz, 1H).
ESI-MS m/z: Calcd. for $C_{39}H_{43}N_5O_8$: 709.8. Found $(M+1)^+$: 710.3.

Example 82



43 88

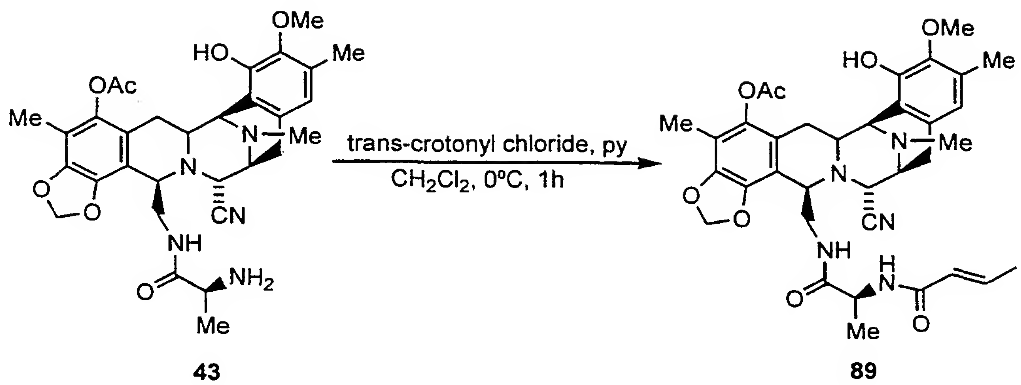
To a solution of **43** (30 mg, 0.05 mmol) in CH_2Cl_2 (0.3 mL), propionyl chloride (4.40 μL, 0.05 mmol) and pyridine (4.04 μL, 0.05 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 1:1 to EtOAc) to afford **88** (18 mg, 56 %) as a white solid.

Rf: 0.49 (Hex:EtOAc:MeOH 1:10:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.16 (brd, 1H), 5.99 (d, J= 1.2 Hz, 1H), 5.95 (s, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.34 brt, 1H), 4.12-4.06 (m, 3H), 3.84 (bs, 1H), 3.74 (s, 3H), 3.63 (dd, J_1= 6.3 Hz, J_2= 12.9 Hz, 1H), 3.50-3.48 (m, 1H), 3.39 (d, J= 8.1 Hz, 1H), 3.23 (d, J= 11.7 Hz, 1H), 3.00 (dd, J_1= 8.4 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 15.6 Hz, 1H), 2.63 (d, J= 18.3 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 1.87-1.80 (m, 1H), 1.06 (t, J= 7.5Hz, 3H), 0.74 (d, J= 6.9 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{34}H_{41}N_5O_8$: 647.7. Found $(M+1)^+$: 648.2.

Example 83



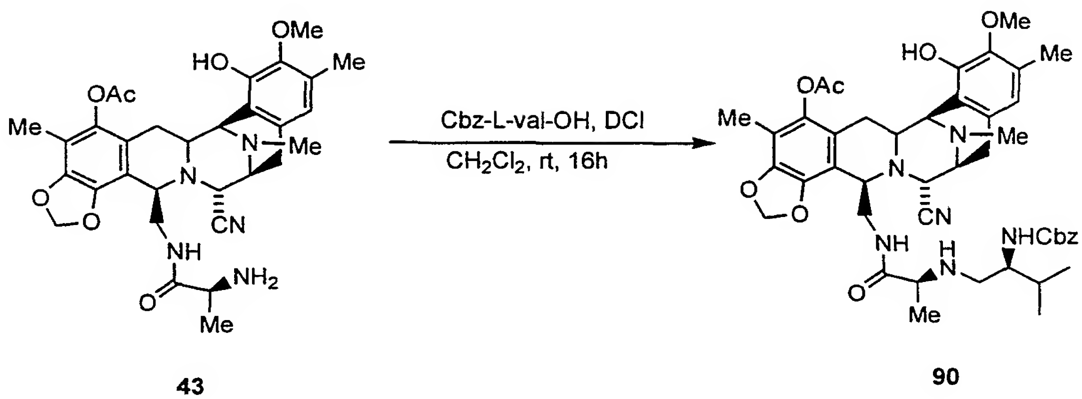
To a solution of **43** (20 mg, 0.0338 mmol) in CH_2Cl_2 (0.3 mL), propionyl chloride (3.238 μL, 0.0338 mmol) and pyridine (2.73 μL, 0.0338 mmol) were added at 0 °C. The reaction mixture was stirred for 1h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 3:1 to AcOEt) to afford **89** (11.5 mg, 52 %) as a white solid.

Rf: 0.57 (EtOAc:MeOH 10:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82-6.70 (m, 1H), 6.46 (s, 1H), 6.11 (d, 1H), 6.00 (d, J= 1.5 Hz, 1H), 5.89 (d, J= 1.5 Hz, 1H), 5.85 (s, 1H), 5.77 (dd, J_1= 1.5 Hz, J_2= 15.3 Hz, 1H), 5.37 (bst, 1H), 4.13-4.06 (m, 3H), 3.19 (m, 1H), 3.73 (s, 3H), 3.55 (m, 2H), 3.38 (d, J= 1.5 Hz, 1H), 3.23 (d, J= 11.4 Hz, 1H), 3.00 (dd, J_1= 8.4 Hz, J_2= 18.3 Hz, 1H), 2.78 (d, J= 15.0 Hz, 1H), 2.65 (d, J= 18.0 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.22 (s, 3H), 2.00 (s, 3H), 1.85-1.82 (m, 4H), 0.77 (d, J= 6.3 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{35}H_{41}N_5O_8$: 659.7. Found $(M+1)^+$: 660.3.

Example 84



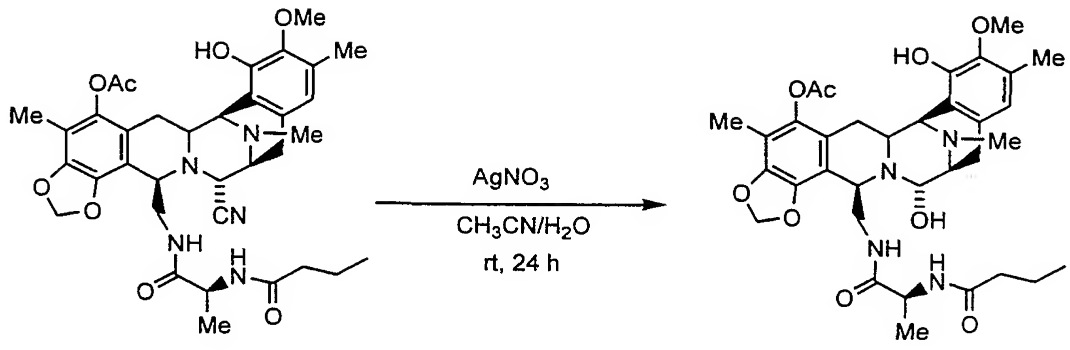
To a solution of **43** (15 mg, 0.0253 mmol) in CH_2Cl_2 (0.3 mL), Cbz-L-Val-OH (6.39 mg, 0.0253 mmol) and carbonyl diimidazole (4.86 mg, 0.03 mmol) were added at 0 °C. The reaction mixture was stirred for 16 h at room temperature and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 1:1 to EtOAc) to afford **90** (6.7 mg, 32 %) as a white solid.

Rf: 0.79 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (bs, 5H), 6.46 (s, 1H), 6.28 (d, *J*= 6.0 Hz, 1H), 5.98 (d, *J*= 1.2 Hz, 1H), 5.89 (d, *J*= 1.2 Hz, 1H), 5.77 (s, 1H), 5.44 (bs, 1H), 5.30 (bs, 1H), 5.08 (s, 2H), 4.09-4.06 (m, 3H), 3.94-3.89 (m, 1H), 3.70-3.66 (m, 5H), 3.38 (d, *J*= 11.7 Hz, 1H), 3.01 96 (dd, J_1= 7.8 Hz, J_2= 18.3 Hz, 1H), 2.79 (d, *J*= 14.1 Hz, 1H), 2.63 (d, *J*= 18.0 Hz, 1H), 2.30 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H), 1.99 (s, 3H9, 1.97-1.81 (m, 2H), 0.83 (d, *J*= 6.6 Hz, 3H), 0.80 (d, *J*= 6.6 Hz, 3H), 0.75 (d, *J*= 6.9 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{44}H_{52}N_6O_{10}$: 824.9. Found $(M+1)^+$: 825.4.

Example 85



62 91

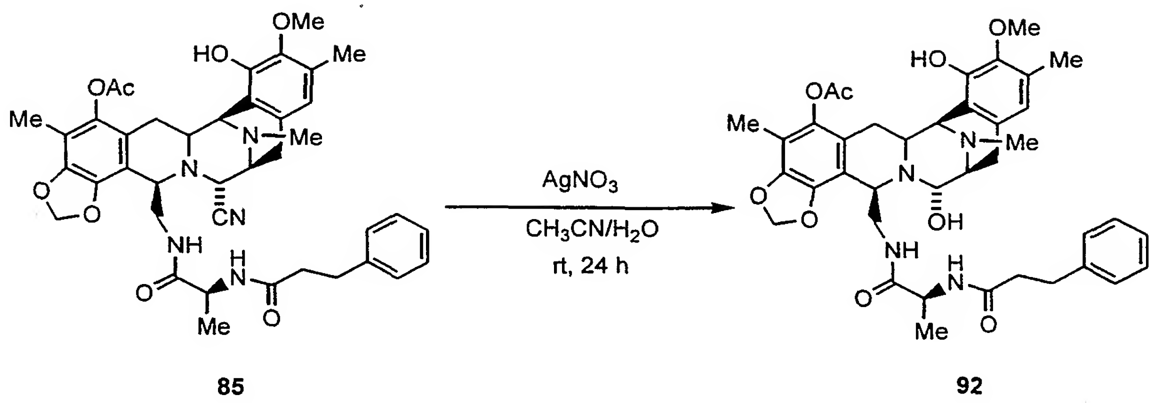
To a solution of **62** (20 mg, 0.030 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (154 mg, 0.90 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 3:1) to afford **91** (13 mg, 66 %) as a white solid.

Rf: 0.18 (EtOAc:MeOH 10:1).

^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.16 (d, 1H), 5.98 (d, J= 1.5 Hz, 1H), 5.89 (d, J= 1.5 Hz, 1H), 5.32 (bs, 1H), 4.41 (bs, 1H), 4.00 (bs, 1H), 3.79 (s, 3H), 3.70-3.65 (m, 2H), 3.37-3.32 (m, 2H), 3.19-3.17 (m, 1H), 2.94 (dd, J_1= 9.0 Hz, J_2= 15.0 Hz, 1H), 2.74 (d, J= 15.9 Hz, 1H), 2.46 (d, J= 17.1 Hz, 1H), 2.31 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H), 2.04-2.01 (m, 2H), 1.98 (s, 3H), 1.64-1.62 (m, 1H), 1.54-1.52 (m, 2H), 0.89-0.84 (m, 6H).

ESI-MS m/z: Calcd. for $C_{34}H_{44}N_4O_9$: 652.7. Found $(M-17)^+$: 635.3.

Example 86



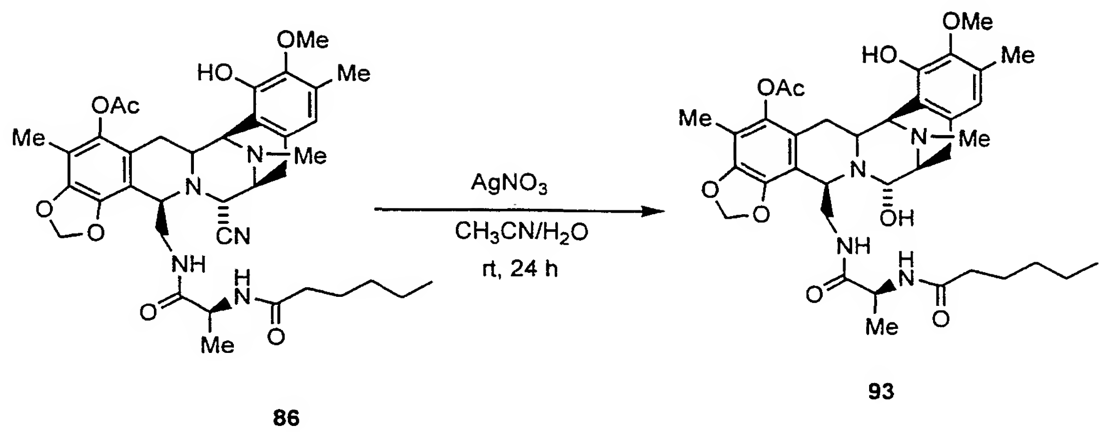
To a solution of **85** (10 mg, 0.0138 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (70.4 mg, 0.414 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 4:1) to afford **92** (7 mg, 71 %) as a white solid.

Rf: 0.20 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.13 (m, 5H), 6.47 (s, 1H), 6.13 (brd, 1H), 5.97 (d, *J*= 1.2 Hz, 1H), 5.88 (d, *J*= 1.2 Hz, 1H), 5.34 (brt, 1H), 4.50 (bs, 1H), 4.40 (bs, 1H), 4.00 (bs, 1H), 3.76 (s, 3H), 3.70-3.65 (m, 3H), 3.34 (d, *J*= 11.7 Hz, 1H), 3.17 (d, *J*= 5.1 Hz, 1H), 2.98-2.83 (m, 3H), 2.72 (d, *J*= 14.4 Hz, 1H), 2.44 (d, *J*= 19.2 Hz, 1H), 2.30 (s, 3H), 2.27 (s, 6H), 1.97 (s, 3H), 1.72 (m, 1H), 0.82 (d, *J*= 6.6 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{39}H_{46}N_4O_9$: 714.8. Found $(M-17)^+$: 697.3.

Example 87



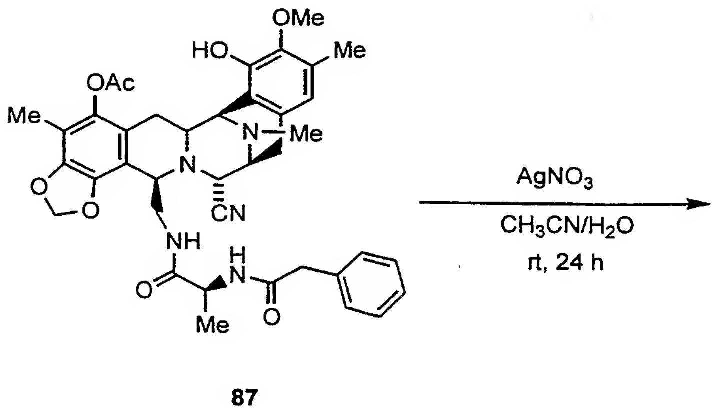
To a solution of **86** (6 mg, 0.0087 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (44 mg, 0.26 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 5:1) to afford **93** (5 mg, 85 %) as a white solid.

Rf: 0.018 (EtOAc:MeOH 5:1).

^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.17 (d, 1H), 5.98 (d, *J*= 1.5 Hz, 1H), 5.89 (d, *J*= 1.5 Hz, 1H), 5.33 (bs, 1H), 4.51 (d, 1H), 4.40 (d, 1H), 4.00 (d, 1H), 3.78 (s, 3H), 3.76-3.65 (m, 2H), 3.36-3.32 (m, 2H), 3.18 (d, *J*= 6.9 Hz, 1H), 2.98-2.89 (m, 1H), 2.71 (d, *J*= 15.0 Hz, 1H), 2.45 (d, *J*= 17.7 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.26 (s, 3H), 1.98 (s, 3H), 1.68-1.50 (m, 3H), 1.29-1.19 (m, 6H), 0.88-0.84 (m, 6H).

ESI-MS m/z: Calcd. for $C_{36}H_{48}N_4O_9$: 680.7. Found $(M-17)^+$: 663.3.

Example 88



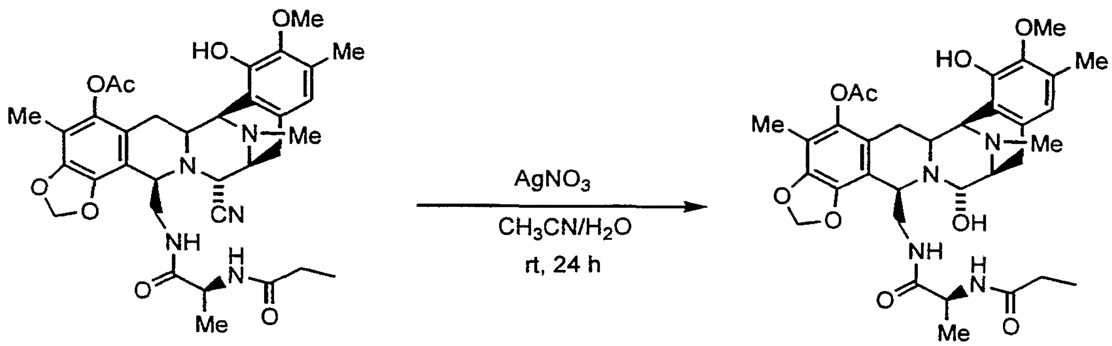
To a solution of **87** (12 mg, 0.0169 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (86 mg, 0.507 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 5:1) to afford **94** (8.8 mg, 74 %) as a white solid.

Rf: 0.28 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.18 (m, 5H), 6.37 (s, 1H), 6.20 (d, 1H), 5.96 (d, J= 1.5 Hz, 1H), 5.88 (d, J= 1.5 Hz, 1H), 5.30 (t, 1H), 4.50 (bs, 1H), 4.39 (d, J= 1.8 Hz, 1H), 3.99 (d, J= 2.1 Hz, 1H), 3.73 (s, 3H), 3.69-3.60 (m, 3H), 3.37-3.30 (m, 3H), 3.17 (d, J= 18.1 Hz, 1H), 2.89 (dd, J_1= 7.5 Hz, J_2= 18.3 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.21 (s, 3H), 1.99 (s, 3H), 1.71 (dd, J_1= 11.7 Hz, J_2= 15.0 Hz, 1H), 0.77 (d, J= 6.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{38}H_{44}N_4O_9$: 700.7. Found $(M-17)^+$: 683.2.

Example 89



88 95

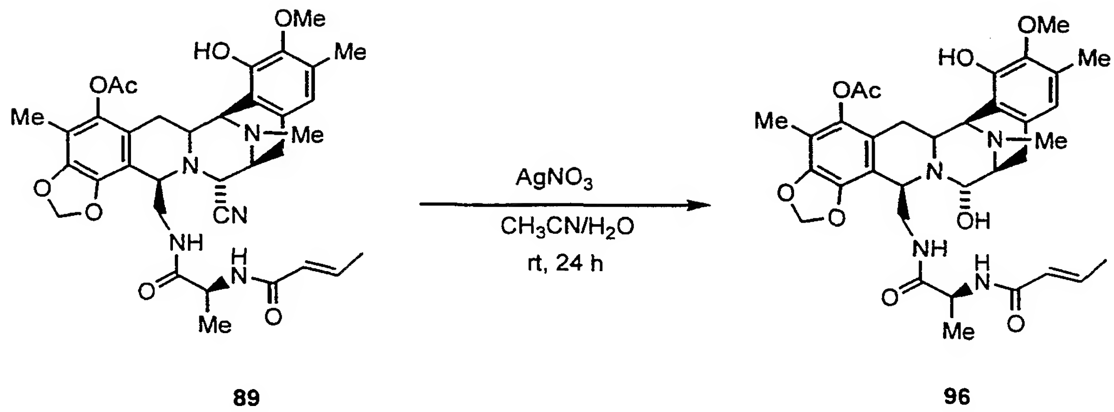
To a solution of **88** (14 mg, 0.0216 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (110 mg, 0.648 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 5:1) to afford **95** (9.7 mg, 70 %) as a white solid.

Rf: 0.16 (EtOAc:MeOH 5:1).

^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (s, 1H), 6.10 (d, 1H), 5.97 (d, *J*= 1.2 Hz, 1H), 5.89 (d, *J*= 1.2 Hz, 1H), 5.36 (bs, 1H), 4.51 (bs, 1H), 4.40 (d, *J*= 2.1 Hz, 1H), 4.00 (d, *J*= 2.1 Hz, 1H), 3.78 (s, 3H), 3.76-3.62 (m, 3H), 3.33 (d, *J*= 11.7Hz, 1H), 3.18 (d, *J*= 8.4 Hz, 1H), 2.94 (dd, J_1= 8.4 Hz, J_2= 16.5 Hz, 1H), 2.72 (d, *J*= 15.0 Hz, 1H), 2.45 (d, *J*= 18.3 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.22 (s, 3H), 1.97 (s, 3H), 1.86 (m, 2H), 1.73 (dd, J_1= 12.0 Hz, J_2= 15.0 Hz, 1H), 1.05 (t, *J*= 7.8 Hz, 3H), 0.83 (d, *J*= 6.9 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{33}H_{42}N_4O_9$: 638.7. Found $(M-17)^+$: 621.2.

Example 90



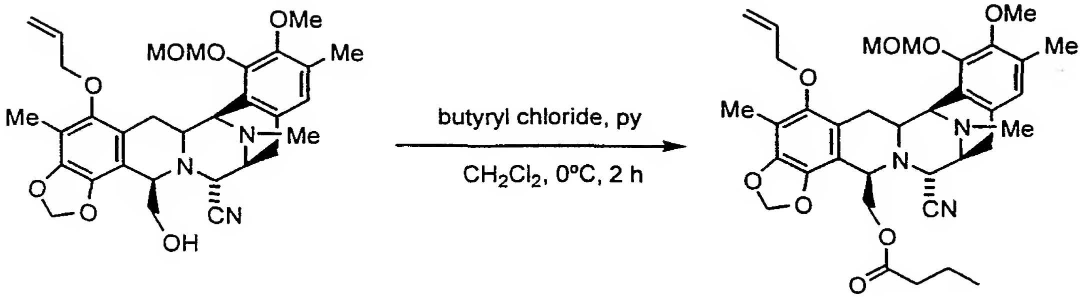
To a solution of **89** (10 mg, 0.015 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (77.2 mg, 0.454 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 1:1) to afford **96** (9 mg, 92 %) as a white solid.

Rf: 0.016 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76-6.69 (m, 1H), 6.47 (s, 1H), 6.18 (brd, 1H), 5.97 (d, *J*= 1.5 Hz, 1H), 5.88 (d, *J*= 1.5 Hz, 1H), 5.71 (dd, J_1= 1.5 Hz, J_2= 16.2 Hz, 3H), 5.32 (bs, 1H), 4.50 (m, 1H), 4.41 (m, 1H), 3.99 (m, 1H), 3.78 (m, 4H), 3.64-3.58 (m, 2H), 3.34 (d, *J*= 11.1 Hz, 1H), 3.17 (d, *J*= 8.6 Hz, 1H), 2.95 (dd, J_1= 7.5 Hz, J_2= 17.4 Hz, 1H), 2.70 (d, *J*= 16.2 Hz, 1H), 2.48 (d, *J*= 17.7 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.17 (s, 6H), 1.97 (s, 3H), 1.82-1.74 (m, 4H), 0.88 (t, *J*= 5.2 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{34}H_{42}N_4O_9$: 650.7. Found $(M-17)^+$: 633.3.

Example 91



25 97

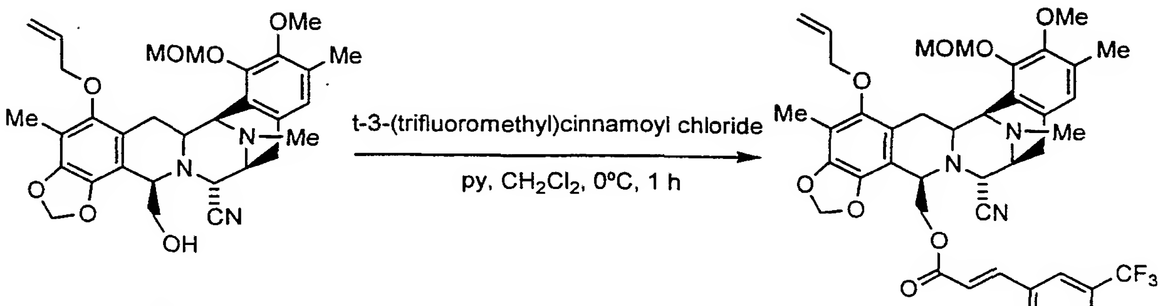
To a solution of **25** (100 mg, 0.177 mmol) in CH_2Cl_2 (0.5 mL), butyryl chloride (24 μL, 0.23 mmol) and pyridine (17 μL, 0.212 mmol) were added at 0 °C. The reaction mixture was stirred for 2h at room temperature and then, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 0.1 N HCl (20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 3:1) to afford **97** (99 mg, 88 %) as a colorless oil.

Rf: 0.64 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.16-6.05 (m, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.87 (d, J= 1.2 Hz, 1H), 5.40 (dd, J_1= 1.2 Hz, J_2= 17.1 Hz, 1H), 5.26 (dd, J_1= 1.2 Hz, J_2= 10.2 Hz, 1H), 5.13-5.08 (m, 2H), 4.44 (dd, J_1= 3.6 Hz, J_2= 11.1 Hz, 1H), 4.21-4.07 (m, 5H), 3.74 (m, 1H), 3.72 (s, 1H), 3.57 (s, 3H), 3.35 (d, . J= 10.5 Hz, 1H), 3.26-3.21 (m, 2H), 3.98 (dd, J_1= 8.7 Hz, J_2= 18.0 Hz, 1H), 2.54 (d, J= 18.0 Hz), 2.30 (s, 3H), 2.21 (s, 3H), 2.13 (s, 3H), 1.92-1.65 (m, 3H), 1.42-1.34 (m, 2H), 0.80 (t, J= 7.5 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{35}H_{43}N_3O_9$: 633.7. Found $(M+1)^+$: 634.3.

Example 92



25

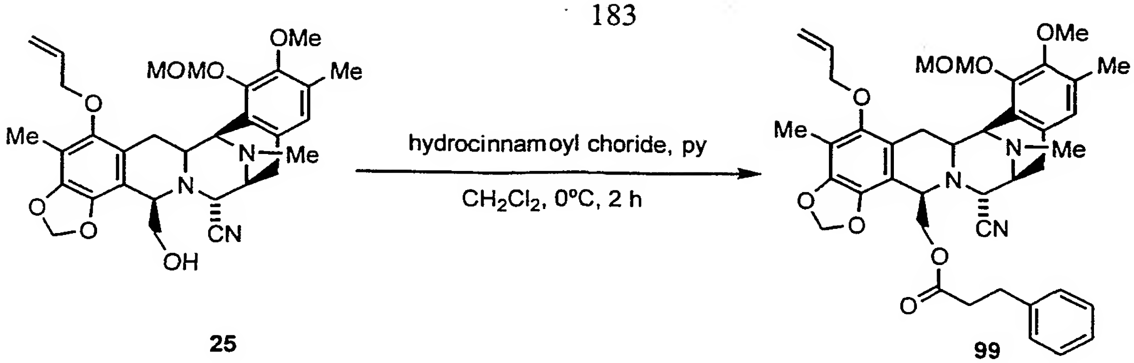
98

To a solution of **25** (100 mg, 0.177 mmol) in CH_2Cl_2 (0.4 mL), trans-3-(trifluoromethyl)cinnamoyl chloride (35 μL, 0.23 mmol) and pyridine (17 μL, 0.212 mmol) were added at 0 °C. The reaction mixture was stirred for 1h at room temperature and then, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 0.1 N HCl (20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 6:1 to Hex:EtOAc 1:1) to afford **98** (122 mg, 90 %) as a white solid. Rf: 0.478 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.64-7.48 (m, 4H), 7.37 (d, J= 15.6 Hz, 1H), 6.62 (s, 1H), 6.16-6.07 (m, 1H), 6.12 (d, J= 15.6 Hz, 1H), 5.94 (d, J= 1.2 Hz, 1H), 5.89 (d, J= 1.2 Hz, 1H), 5.41 (dd, J_1= 1.8 Hz, J_2= 17.1 Hz, 1H), 5.28 (dd, J_1= 1.8 Hz, J_2= 12.0 Hz, 1H), 5.04 (q, J= 6.0 Hz, 1H), 4.60 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 4.22-4.15 (m, 5H), 3.90 (dd, J_1= 4.2 Hz, J_2= 11.1 Hz, 1H), 3.55 (s, 3H), 3.38 (s, 3H), 3.35-3.34 (m, 1H), 3.27-3.25 (m, 1H), 3.22 (bs, 1H), 2.98 (dd, J_1= 7.8 Hz, J_2= 18.0 Hz, 1H), 2.61 (d, J= 17.7 Hz, 1H), 2.29 (s, 3H), 2.16 (s, 3H), 2.00 (s, 3H), 1.80 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{41}H_{42}F_3N_3O_8$: 761.7. Found $(M+1)^+$: 762.3.

Example 93



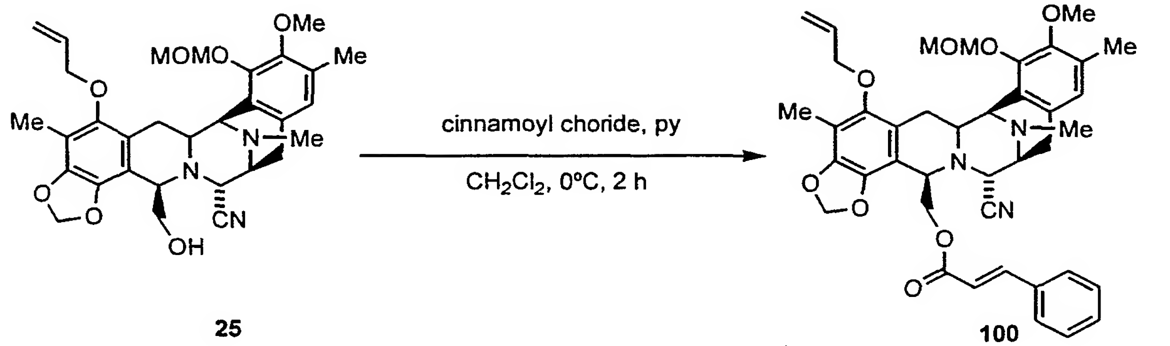
25 99

To a solution of **25** (68 mg, 0.12 mmol) in CH_2Cl_2 (0.4 mL), hydrocynnamoyl chloride (20 μL, 1.12 mmol) and pyridine (10 μL, 1.01 mmol) were added at 0 °C. The reaction mixture was stirred for 2h at room temperature and then, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 0.1 N HCl (20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 5:1 to Hex:EtOAc 2:1) to afford **99** (41 mg, 49 %) as a white solid. Rf: 0.47 (Hex:EtOAc 1:1).

^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.18 (m, 3H), 7.04-7.02 (m, 2H), 6.66 (s, 1H), 6.16-6.07 (m, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.87 (d, J= 1.2 Hz, 1H), 5.40 (dd, J_1= 1.7 Hz, J_2= 17.4 Hz, 1H), 5.26 (dd, J_1= 1.7 Hz, J_2= 10.2 Hz, 1H), 5.09 (dd, J_1= 6.0 Hz, J_2= 8.7 Hz, 2H), 4.43 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 4.20-4.14 (m, 3H), 4.06 (t, J= 3.7 Hz, 1H), 4.02 (d, J= 2.4 Hz, 1H), 3.72 (dd, J_1= 4.5 Hz, J_2= 11.1 Hz, 1H), 3.56 (s, 3H), 3.55 (s, 3H), 3.32 (brd, J= 8.7 Hz, 1H), 3.26 (dd, J_1= 1.9 Hz, J_2= 8.1 Hz, 1H), 3.23-3.20 (m, 1H), 3.01 (brd, J= 8.1 Hz, 1H), 3.23-3.20 (m, 1H), 3.26 (dd, J_1= 1.9 Hz, J_2= 8.1 Hz, 1H), 2.95 (d, J= 1.8 Hz, 1H), 2.71-2.64 (m, 3H), 2.53 (d, J= 17.7 Hz, 1H), 2.26 (s, 3H), 2.14 (s, 6H), 1.83 (dd, J_1= 12.3 Hz, J_2= 15.9 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{40}H_{45}F_3N_3O_8$: 695.3. Found $(M+1)^+$: 696.3.

Example 94

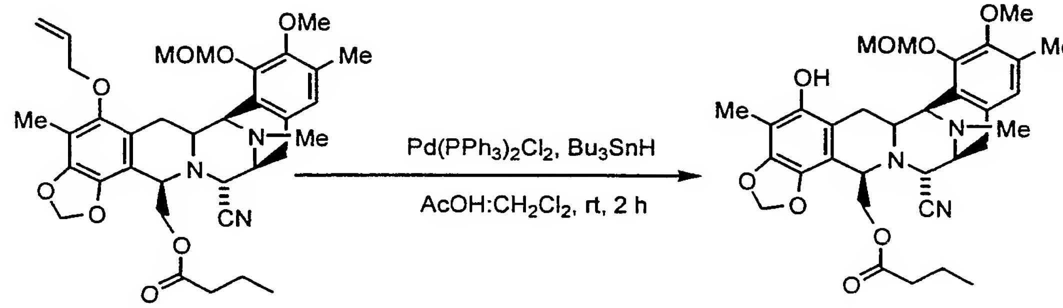


To a solution of **25** (100 mg, 0.177 mmol) in CH_2Cl_2 (0.4 mL), cynnamoyl chloride (35 mg, 0.21 mmol) and pyridine (17 µL, 0.21 mmol) were added at 0 °C. The reaction mixture was stirred for 2h at room temperature and then, the solution was diluted with CH_2Cl_2 (30 mL) and washed with 0.1 N HCl (20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 6:1) to afford **100** (94 mg, 76 %) as a white solid. Rf: 0.49 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42-7.33 (m, 6H), 6.62 (s, 1H), 6.16-6.05 (m, 1H), 6.10 (d, J= 15.9Hz, 1H), 5.94 (d, J= 1.2 Hz, 1H), 5.88 (d, J= 1.2 Hz, 1H), 5.43 (dd, J_1= 3.0 Hz, J_2= 17.1 Hz, 1H), 5.27 (dd, J_1= 3.0 Hz, J_2= 12.0 Hz, 1H), 5.04 (q, J= 6.0 Hz, 1H), 4.55 (dd, J_1= 3.9 Hz, J_2= 11.1 Hz, 1H), 4.22-4.15 (m, 5H), 3.87 (dd, J_1= 4.5 Hz, J_2= 11.1 Hz, 1H), 3.55 (s, 3H), 3.39 (s, 3H), 3.36-3.33 (m, 1H), 3.26-3.22 (m, 2H), 2.98 (dd, J_1= 8.1 Hz, J_2= 17.7 Hz, 1H), 2.63 (d, J= 17.7 Hz, 1H), 2.29 (s, 3H), 2.03 (s, 3H), 1.82 (dd, J_1= 11.7 Hz, J_2= 15.3Hz, 1H).

ESI-MS m/z: Calcd. for $C_{40}H_{43}N_3O_8$: 693.3. Found $(M+1)^+$: 694.3.

Example 95



97

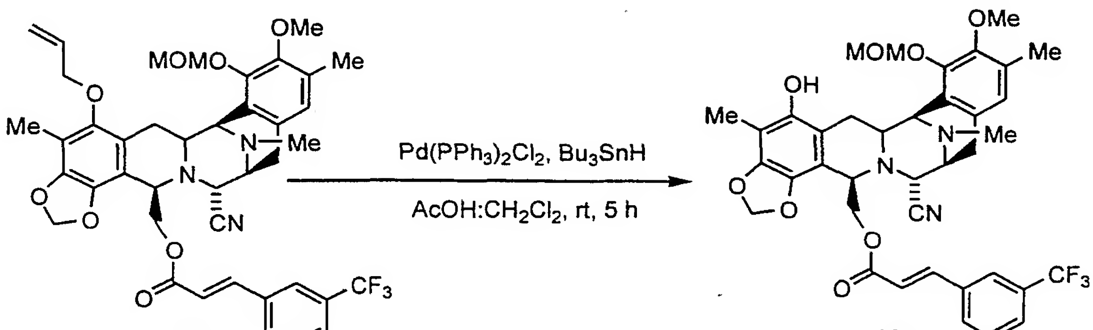
101

To a solution of **97** (40 mg, 0.063 mmol) in CH_2Cl_2 (0.7 mL), acetic acid (17.8 μL), $Pd(PPh_3)_2Cl_2$ (3.64 mg, 0.0052 mmol) and Bu_3SnH (67.9 μL, 0.252 mmol) were added at 23 °C. The reaction mixture was stirred for 2h at that temperature and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 5:1 to Hex:EtOAc 3:1) to afford **101** (30 mg, 80 %) as a white solid. Rf: 0.4 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.65 (s, 1H), 5.90 (d, *J*= 1.5 Hz, 1H), 5.82 (d, *J*= 1.5 Hz, 1H), 5.54 (s, 1H), 5.33 (d, *J*= 6.0 Hz, 1H), 5.13 (d, *J*= 6.0 Hz, 1H), 4.54 (dd, J_1= 3.6 Hz, J_2= 11.4 Hz, 1H), 4.18 (d, *J*= 2.1 Hz, 1H), 4.13 (d, *J*= 2.4 Hz, 1H), 4.07 (t, *J*= 3.3 Hz, 1H), 3.75 (dd, J_1= 3.9 Hz, J_2= 11.1 Hz, 1H), 3.70 (s, 3H), 3.35 (d, *J*= 8.4 Hz, 1H), 3.24 (dd, J_1= 2.7 Hz, J_2= 8.7 Hz, 1H), 3.10 (dd, J_1= 2.4 Hz, J_2= 15.0 Hz, 1H), 3.01 (d, *J*= 8.1 Hz, 1H), 2.95 (d, *J*= 7.8 Hz, 1H), 2.58 (d, *J*= 18.3 Hz, 1H), 2.29 (s, 3H), 2.21 (s, 3H), 2.10 (s, 3H), 1.89-1.66 (m, 3H), 1.36-1.25 (m, 2H), 0.77 (t, *J*= 7.5 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{32}H_{39}N_3O_8$: 593.6. Found $(M+1)^+$: 594.8

Example 96



98

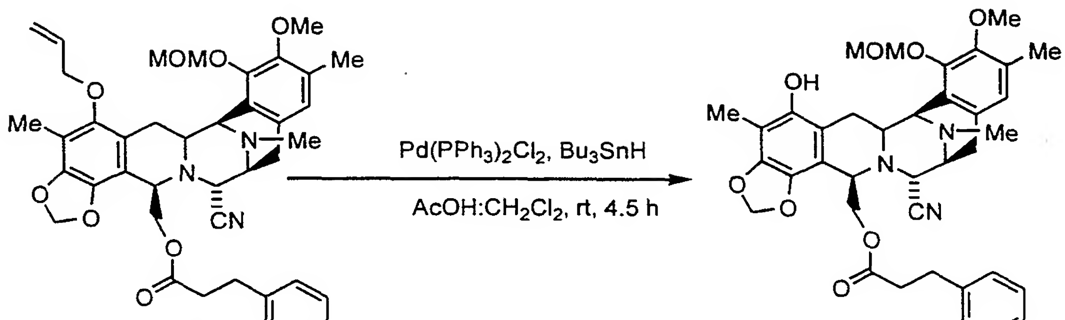
102

To a solution of **98** (37 mg, 0.0485 mmol) in CH_2Cl_2 (0.7 mL), acetic acid (20 μL), $Pd(PPh_3)_2Cl_2$ (4 mg, 0.0057 mmol) and Bu_3SnH (53 μL, 0.194 mmol) were added at 23 °C. The reaction mixture was stirred for 5h at that temperature and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 6:1 to Hex:EtOAc 2:1) to afford **102** (25 mg, 71 %) as a white solid. Rf: 0.38 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.63-7.60 (M, 2H), 7.50-7.49 (M, 2H), 7.24 (d, J= 15.9 Hz, 1H), 6.59 (s, 1H), 5.98 (d, J= 15.9 Hz, 1H), 5.92 (d, J= 1.5 Hz, 1H), 5.84 (d, J= 1.5 Hz, 1H), 5.66 (s, 1H), 5.20 (d, J= 6.0 Hz, 1H), 4.87 (d, J= 6.0 Hz, 1H), 4.71 (dd, J_1= 2.7 Hz, J_2= 10.8 Hz, 1H), 4.16-4.15 (m, 3H), 3.93 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 3.66 (s, 3H), 3.36 (brd, J= 10.2 Hz, 1H), 3.26 (brd, J= 11.7 Hz, 1H), 3.10 (brd, J= 15.0 Hz, 1H), 2.96 (dd, J_1= 7.8 Hz, J_2= 17.7 Hz, 1H), 2.62 (d, J= 17.7 Hz, 1H), 2.27 (s, 3H), 2.14 (s, 3H), 1.97 (s, 3H), 1.79 (dd, J_1= 12.0 Hz, J_2= 15.8 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{38}H_{38}F_3N_3O_8$: 721.7. Found $(M+1)^+$: 722.2.

Example 97

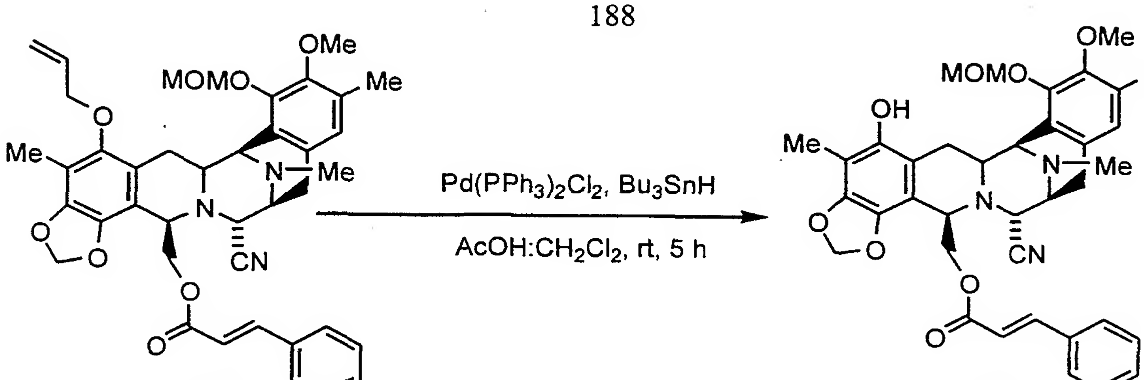


99 103

To a solution of **99** (41 mg, 0.059 mmol) in CH_2Cl_2 (1 mL), acetic acid (25 μL), $Pd(PPh_3)_2Cl_2$ (5 mg, 0.0071 mmol) and Bu_3SnH (63 μL, 0.235 mmol) were added at 23 °C. The reaction mixture was stirred for 4.5 h at that temperature and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 6:1 to Hex:EtOAc 1:1) to afford **103** (34.2 mg, 89 %) as a white solid. Rf: 0.49 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (m, 3H), 7.03-7.01 (m, 2H), 6.65 (s, 1H), 5.89 (bs, 1H), 5.82 (bs, 1H), 5.49 (s, 1H), 5.31 (d, *J*= 6.0 Hz, 1H), 5.12 (d, *J*= 6.0 Hz, 1H), 4.53 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 4.18 (d, *J*= 2.7 Hz, 1H), 4.07 (m, 2H), 3.75 (dd, J_1= 3.9 Hz, J_2= 11.1 Hz, 1H), 3.69 (s, 3H), 3.62 (s, 3H), 3.32 (d, *J*= 7.8 Hz, 1H), 3.25 (d, *J*= 10.8 Hz, 1H), 3.12 (d, *J*= 14.7Hz, 1H), 3.00 (d, *J*= 7.8 Hz, 1H), 2.94 (d, *J*= 8.1 Hz, 1H), 2.66-2.60 (m, 3H), 2.57 (d, *J*= 18.0 Hz, 1H), 2.28 (s, 3H), 2.14 (s, 3H), 2.10 (bs, 3H), 1.83-1.74 (m, 1H).
ESI-MS m/z: Calcd. for $C_{37}H_{41}N_3O_8$: 655.7. Found $(M+1)^+$: 656.3.

Example 98

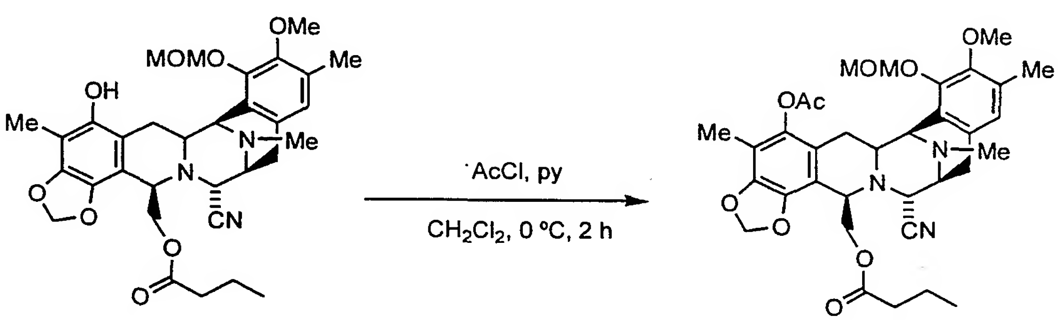


To a solution of **100** (40 mg, 0.0576 mmol) in CH_2Cl_2 (1 mL), acetic acid (25 μL), $Pd(PPh_3)_2Cl_2$ (4.8 mg, 0.007 mmol) and Bu_3SnH (62 μL, 0.23 mmol) were added at 23 °C. The reaction mixture was stirred for 5 h at that temperature and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 4:1 to Hex:EtOAc 1:1) to afford **104** (30 mg, 82 %) as a white solid. Rf: 0.41 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (s, 5H), 7.30 (d, J= 16.2 Hz, 1H), 6.59 (s, 1H), 5.99 (d, J= 16.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.84 (d, J= 1.2 Hz, 1H), 5.60 (s, 1H), 5.20 (d, J= 5.6 Hz, 1H), 4.94 (d, J= 5.6 Hz, 1H), 4.63 (dd, J_1= 3.3 Hz, J_2= 11.4 Hz, 1H), 4.18-4.15 (m, 3H), 3.91 (dd, J_1= 3.9 Hz, J_2= 11.1 Hz, 1H), 3.66 (s, 3H), 3.49 (s, 3H), 3.35 (brd, J= 15.0 Hz, 1H), 3.26 (brd, J= 11.4 Hz, 1H), 3.10 (brd, J= 15.0 Hz, 1H), 2.96 (dd, J_1= 8.4 Hz, J_2= 18.0 Hz, 1H), 2.63 (d, J= 18.0 Hz, 1H), 2.27 (s, 3H), 2.13 (s, 3H), 2.00 (s, 3H), 1.80 (dd, J_1= 12.0Hz, J_2= 14.4 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{37}H_{39}N_3O_8$: 653.7. Found $(M+23)^+$: 676.2.

Example 99



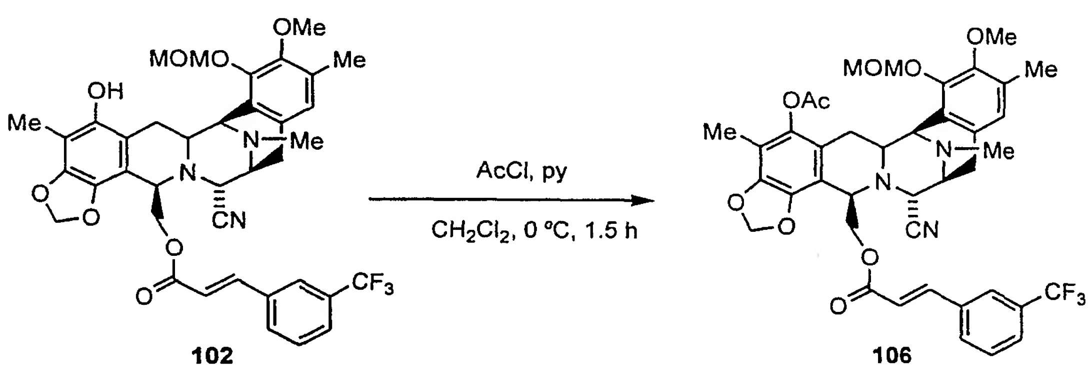
101 105

To a solution of **101** (24 mg, 0.041 mmol) in CH_2Cl_2 (0.4 mL), acetyl chloride (3 μL,

0.041 mmol), and pyridine (3.3 μL, 0.041 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 5:1 to Hex:EtOAc 1:1) to afford **105** (23 mg, 88 %) as a white solid. Rf: 0.40 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.66 (s, 1H), 5.97 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 4.58 (d, J= 3.0 Hz, 1H), 4.54 (d, J= 3.0 Hz, 1H), 4.07 (t, J= 3.3 Hz, 1H), 3.77 (dd, J_1= 3.9 Hz, J_2= 11.4 Hz, 1H), 3.73 (s, 3H), 3.57 (s, 3H), 3.35 (d, J= 10.2 Hz, 1H), 3.22 (dt, J_1= 2.7 Hz, J_2= 11.7 Hz, 1H), 2.98 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.80 (d, J= 13.5 Hz, 1H), 2.58 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.30 (s, 3H), 2.21 (s, 3H), 2.02 (s, 3H), 1.89-1.76 (m, 2H), 1.72-1.66 (m, 1H), 1.37-1.25 (m, 2H), 0.78 (t, J= 7.5 Hz, 3H).
ESI-MS m/z: Calcd. for $C_{34}H_{41}N_3O_9$: 635.7. Found $(M+1)^+$: 636.8.

Example 100

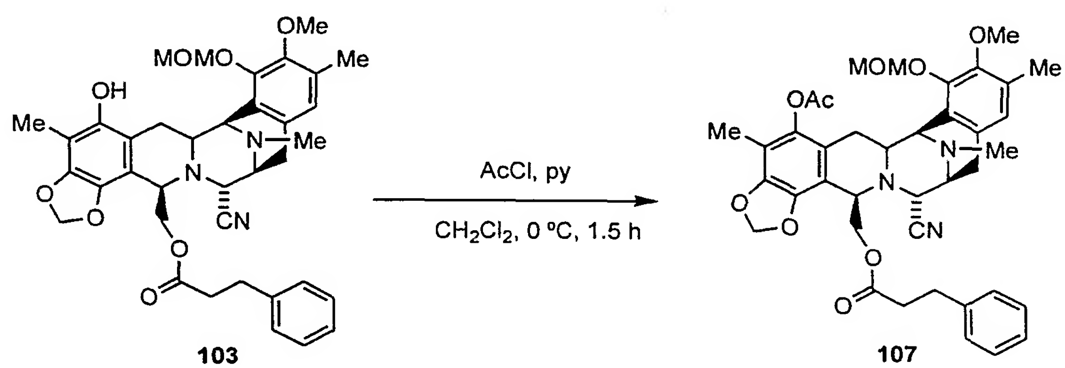


To a solution of **102** (16 mg, 0.022 mmol) in CH_2Cl_2 (0.2 mL), acetyl chloride (1.9 μL, 0.0266 mmol), and pyridine (2.15 μL, 0.0266 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 4:1 toEtOAc) to afford **106** (12 mg, 71

%) as a white solid. Rf: 0.60 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (bs, 1H), 7.65-7.58 (m, 2H), 7.49-7.44 (m, 1H), 7.14 (d, J= 16.2 Hz, 1H), 6.62 (s, 1H), 6.06 (d, J= 16.2 Hz, 1H), 6.00 (d, J= 1.2 Hz, 1H), 5.95 (d, J= 1.2 Hz, 1H), 5.02 (d, J= 5.7 Hz, 1H), 4.96 (bs, 1H), 4.92 (d, J= 5.7 Hz, 1H), 4.15-4.11 (m, 3H), 3.88 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 3.08 (bs, 3H), 2.93 (dd, J_1= 8.1 Hz, J_2= 18.3 Hz, 1H), 2.80 (d, J= 13.2 Hz, 1H), 2.64 (d, J= 18.0 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 2.08 (s, 3H), 1.91 (s, 3H), 1.69 (dd, J_1= 11.7 Hz, J_2= 15.9 Hz, 1H).).
ESI-MS m/z: Calcd. for $C_{40}H_{40}F_3N_3O_9$: 763.7. Found $(M+1)^+$: 764.2.

Example 101



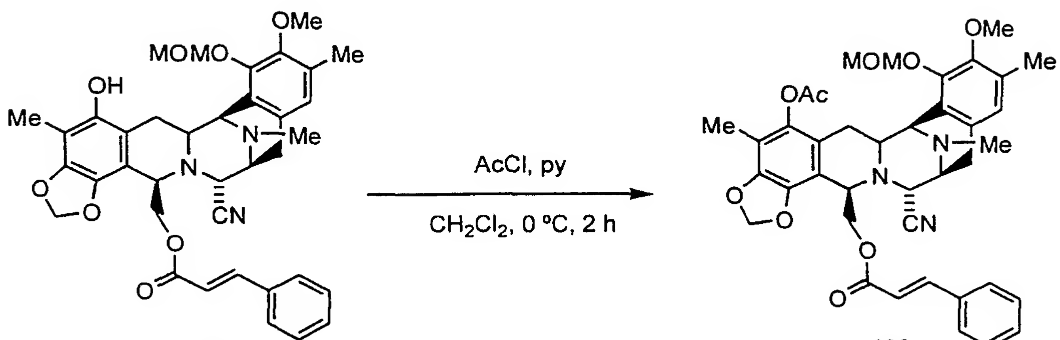
To a solution of **103** (34 mg, 0.052 mmol) in CH_2Cl_2 (0.2 mL), acetyl chloride (4.4 μL, 0.062 mmol), and pyridine (5 μL, 0.062 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 4:1 toEtOAc) to afford **107** (25.5 mg, 70 %) as a white solid. Rf: 0.48 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.14 (m, 3H), 7.06-7.04 (m, 2H), 6.66 (s, 1H), 5.96 (d, J= 1.2 Hz, 1H), 5.91 (d, J= 1.2 Hz, 1H), 5.11 (d, J= 5.4 Hz, 1H), 4.14 (d, J= 3.3 Hz, 1H), 4.07 (d, J= 3.6 Hz, 1H), 4.04 (d, J= 2.7Hz, 1H), 3.78 (dd, J_1= 3.3 Hz, J_2= 10.8 Hz, 1H), 3.55 (s, 3H), 3.51 (s, 3H), 3.33 (brd, J= 8.1 Hz, 1H), 3.23 (dt, J_1= 2.7 Hz, J_2= 11.7 Hz, 1H), 2.97

(dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.81 (d, J= 14.1 Hz, 1H), 2.63-2.52 (m, 3H), 2.33 (s, 3H), 2.29 (s, 3H), 2.26-202 (m, 2H), 2.09 (s, 3H), 2.04 (s, 3H), 1.74 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{39}H_{43}N_3O_9$: 697.7. Found $(M+1)^+$: 698.3.

Example 102

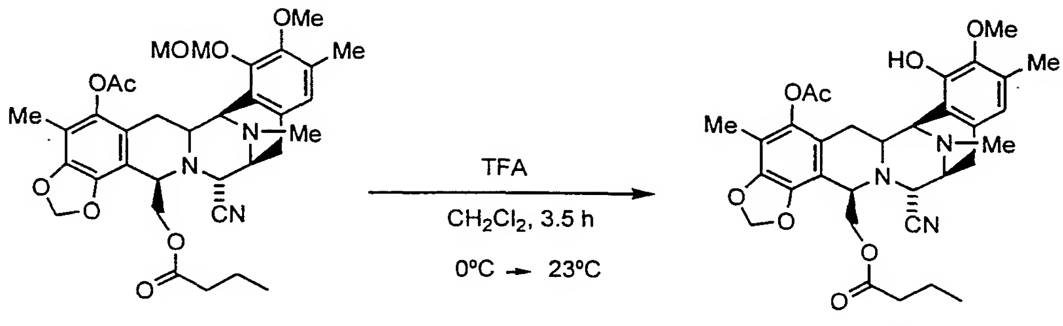


To a solution of **104** (29 mg, 0.0443 mmol) in CH_2Cl_2 (0.3 mL), acetyl chloride (3.77 µL, 0.053 mmol), and pyridine (4.3 µL, 0.053 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 4:1 toEtOAc) to afford **108** (21.6 mg, 70 %) as a white solid. Rf: 0.58 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47-7.44 (m, 2H), 7.35-7.34 (m, 3H), 7.29 (d, J= 15.9 Hz, 1H), 6.62 (s, 1H), 5.99 (d, J= 1.2 Hz, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.05 (d, J= 5.7 Hz, 1H), 4.94 (d, J= 5.7Hz, 1H), 4.81 (d, J= 11.5 Hz, 1H), 4.16-4.11 (m, 3H), 3.34 (brd, J= 5.4 Hz, 1H), 3.24 (bs, 3H), 3.22-3.20 (m, 2H), 2.94 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.80 (d, J= 14.1 Hz, 1H), 2.64 (d, J= 18.0 Hz, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.09 (s, 3H), 1.94 (s, 3H), 1.71 (dd, J_1= 11.7 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{39}H_{41}N_3O_9$: 695.7. Found $(M+1)^+$: 696.2.

Example 103

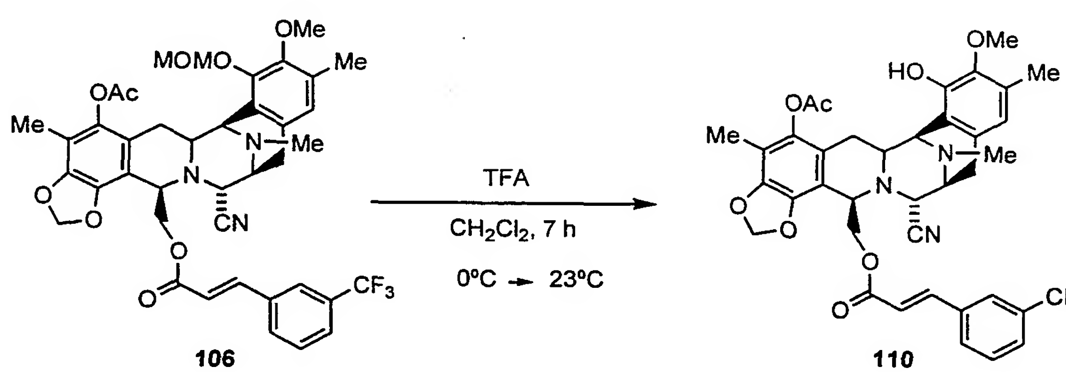


105 109

To a solution of **105** (16 mg, 0.025 mmol) in CH_2Cl_2 (0.2 mL), trifluoroacetic acid (77 µL, 1 mmol) was added at 0 °C and the reaction mixture was stirred for 3.5 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 1:1) to afford **109** (12 mg, 81 %) as a white solid. Rf: 0.32 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.97 (d, J= 1.5 Hz, 1H), 5.91 (d, J= 1.5 Hz, 1H), 5.69 (s, 1H), 4.51 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 4.10-4.05 (m, 3H), 3.78-3.77 (m, 1H), 3.75 (s, 3H), 3.33 (d, J= 8.1 Hz, 1H), 3.22 (dt, J_1= 2.7 Hz, J_2= 12.0 Hz, 1H), 2.96 (dd, J_1= 8.4 Hz, J_2= 17.7 Hz, 1H), 2.80 (d, J= 15.6 Hz, 1H), 2.55 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.01 (s, 3H), 1.87-1.66 (m, 3H), 1.37-1.27 (m, 2H), 0.77 (t, J= 7.5 Hz, 3H). ESI-MS m/z: Calcd. for $C_{32}H_{31}N_3O_8$: 591.6. Found $(M+1)^+$: 592.8.

Example 104



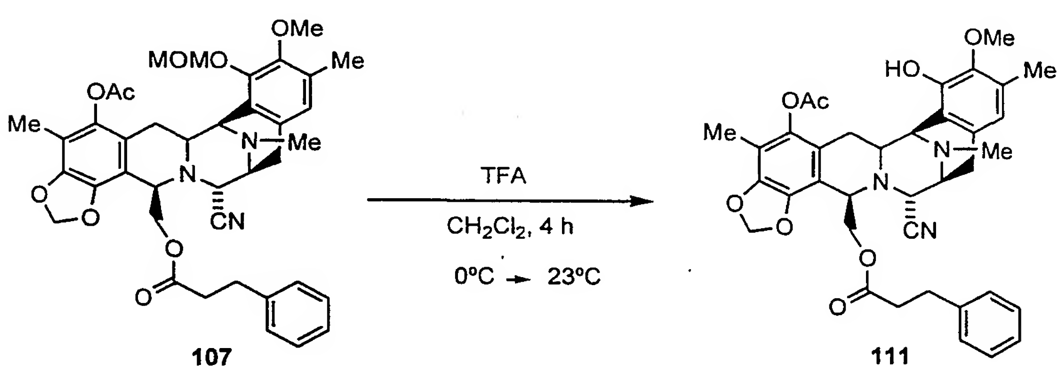
106 110

To a solution of **106** (90 mg, 0.1178 mmol) in CH_2Cl_2 (0.3 mL), trifluoroacetic acid (750 μL, 4.71 mmol) was added at 0 °C and the reaction mixture was stirred for 7 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (20 mL) and extracted with ethyl acetate (2 x 15 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 1:1) to afford **110** (71 mg, 84 %) as a white solid. Rf: 0.6 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.76 (bs, 1H), 7.62-7.57 (m, 2H), 7.48-7.45 (m, 1H), 7.12 (d, *J*= 16.2 Hz, 1H), 6.37 (s, 1H), 6.00 (d, *J*= 16.2 Hz, 1H), 5.98 (d, *J*= 1.2 Hz, 1H), 5.92 (d, *J*= 1.2 Hz, 1H), 5.60 (bs, 1H), 4.88 (d, *J*= 10.2 Hz, 1H), 4.14 (bs, 1H), 4.10 (d, *J*= 2.4 Hz, 1H), 4.03 (d, *J*= 2.4 Hz, 1H), 3.89 (dd, J_1= 2.7 Hz, J_2= 11.4 Hz, 1H), 3.32 (d, *J*= 8.4 Hz, 1H), 3.26-3.21 (m, 4H), 2.91 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.82 (d, *J*= 13.8 Hz, 1H), 2.58 (d, *J*= 18.0 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.05 (s, 3H), 1.89 (s, 3H), 1.84 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{38}H_{36}F_3N_3O_8$: 719.7. Found $(M+1)^+$: 720.3.

Example 105

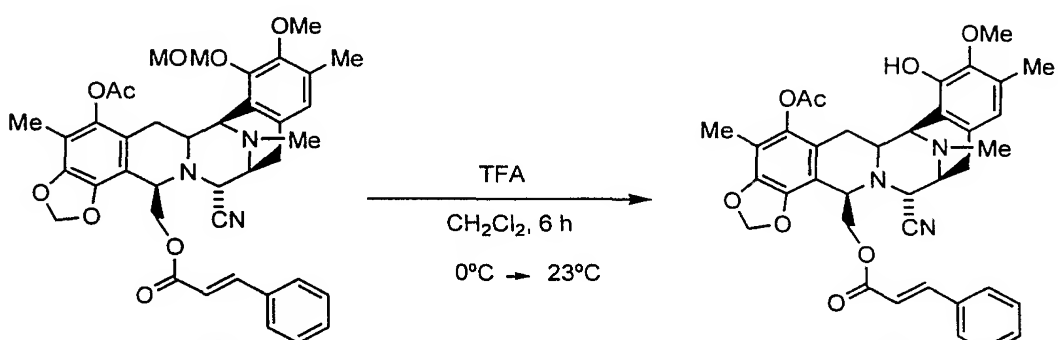


To a solution of **107** (20 mg, 0.286 mmol) in CH_2Cl_2 (0.2 mL), trifluoroacetic acid

(88 µL, 1.144 mmol) was added at 0 °C and the reaction mixture was stirred for 4 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 1:1) to afford **111** (18 mg, 96 %) as a white solid. Rf: 0.39 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.16 (m, 3H), 7.06-7.04 (m, 2H), 6.43 (s, 1H), 5.96 (d, J= 1.5 Hz, 1H), 5.90 (d, J= 1.5 Hz, 1H), 6.66 (s, 1H), 4.52 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 4.07 (s, 1H), 4.05 (d, J= 3.3 Hz, 1H), 4.03 (d, J= 2.4 Hz, 1H), 3.76 (dd, J_1= 3.6 Hz, J_2= 11.1 Hz, 1H), 3.56 (s, 3H), 3.31 (d, J= 7.5 Hz, 1H), 3.23 (d, J= 12.0 Hz, 1H), 2.95 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.80 (d, J= 15.3 Hz, 1H), 2.63-2.58 (m, 2H), 2.53 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.61 (s, 3H), 2.21-2.09 (m, 2H), 2.13 (s, 3H), 2.02 (s, 3H), 1.85 (dd, J_1= 11.7 Hz, J_2= 115.3Hz, 1H). ESI-MS m/z: Calcd. for $C_{37}H_{39}N_3O_8$: 653.7. Found $(M+1)^+$: 654.3.

Example 106



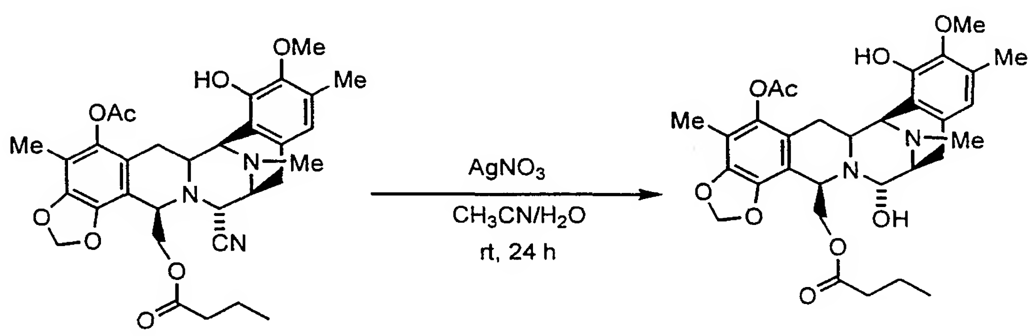
108 **112**

To a solution of **108** (14 mg, 0.02 mmol) in CH_2Cl_2 (0.4 mL), trifluoroacetic acid (61.5 µL, 0.8 mmol) was added at 0 °C and the reaction mixture was stirred for 6 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 2:1) to afford **112** (12 mg, 92 %) as a white solid. Rf: 0.36 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46-7.45 (m, 2H), 7.35-7.20 (m, 4H), 6.38 (s, 1H), 6.05 (d, *J*= 15.9 Hz, 1H), 5.98 (d, *J*= 1.2 Hz, 1H), 5.93 (d, *J*= 1.2 Hz, 1H), 5.57 (s, 1H), 4.71 (d, *J*= 9.3 Hz, 1H), 4.17-4.13 (m, 2H), 4.08 (d, *J*= 1.9 Hz, 1H), 3.89 (dd, J_1= 3.6 Hz, J_2= 11.4 Hz, 1H), 3.33 (m, 5H), 3.26-3.22 (m, 1H), 2.93 (dd, J_1= 9.0 Hz, J_2= 17.4 Hz, 1H), 2.34 (s, 3H), 2.25 (s, 3H), 2.05 (s, 3H), 1.97 (s, 3H), 1.81 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{37}H_{37}N_3O_8$: 651. Found $(M+1)^+$: 652.2.

Example 107



109 113

To a solution of **109** (10 mg, 0.017 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (86 mg, 0.5 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 3:1) to afford **113** (7 mg, 71 %) as a white solid.

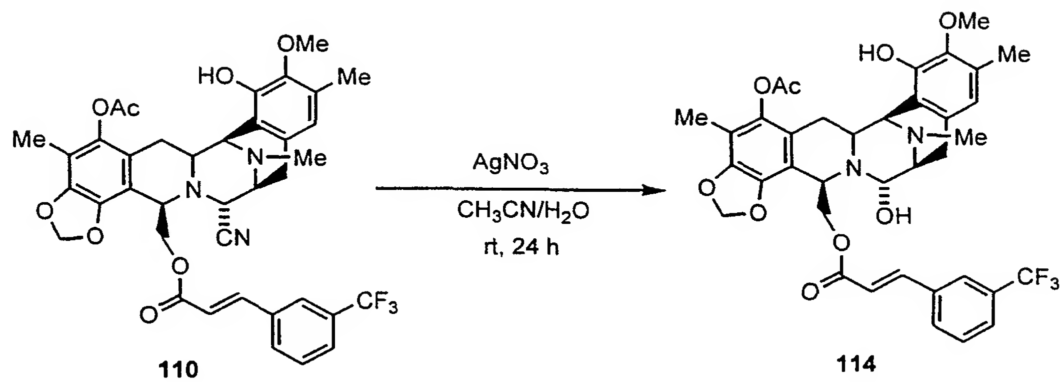
Rf: 0.41 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H), 5.95 (d, *J*= 1.5 Hz, 1H), 5.88 (d, *J*= 1.5 Hz, 1H), 5.65 (bs, 1H), 4.50-4.48 (m, 2H), 4.44 (d, *J*= 2.1 Hz, 1H), 3.96 (d, *J*= 3.0 Hz, 1H), 3.76 (s, 3H), 3.74-3.70 (m, 1H), 3.30 (d, *J*= 12.3 Hz, 1H), 3.13 (d, *J*= 7.5 Hz, 1H), 2.86 (dd, J_1= 5.7 Hz, J_2= 18.3 Hz, 1H), 2.73 (d, *J*= 14.7 Hz, 1H), 2.48 (d, *J*= 17.7 Hz, 1H), 2.33 (s, 3H), 2.24 (s, 3H), 2.17 (s, 3H), 2.00 (s, 3H), 1.86-1.55 (m, 3H), 1.42-1.23 (m, 2H), 0.75 (t, *J*= 7.5 Hz,

3H).

ESI-MS m/z: Calcd. for $C_{31}H_{38}N_2O_9$: 582.6. Found $(M-17)^+$: 565.3.

Example 108



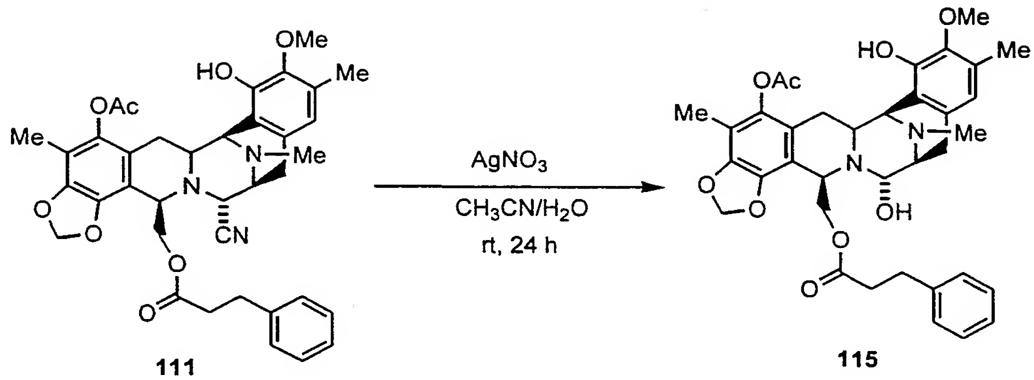
To a solution of **110** (42.8 mg, 0.059 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (303 mg, 1.78 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 5:1) to afford **114** (30 mg, 71 %) as a white solid.

Rf: 0.30 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (bs, 1H), 7.61-7.56 (m, 2H), 7.45-7.42 (m, 1H), 7.12 (d, J= 16.2 Hz, 1H), 6.38 (s, 1H), 6.02 (d, J= 16.2 Hz, 1H), 5.97 (d, J= 1.5 Hz, 1H), 5.90 (d, J= 1.5 Hz, 1H), 5.50 (bs, 1H), 4.87 (bs, 1H), 4.56 (m, 1H), 4.45 (bs, 1H), 3.92 (d, J= 2.4 Hz, 1H), 3.31 (dt, J_1= 3.6 Hz, J_2= 12.9 Hz, 1H), 3.21 (bs, 3H), 3.13 (d, J= 7.8 Hz, 1H), 2.82 (dd, J_1= 8.1 Hz, J_2= 18.0 Hz, 1H), 2.75 (d, J= 14.7 Hz, 1H), 2.49 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.21 (s, 3H), 2.05 (s, 3H), 1.89 (s, 3H), 1.78 (dd, J_1= 12.0 Hz, J_2= 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{37}H_{37}F_3N_2O_9$: 710.6. Found $(M-17)^+$: 693.2.

Example 109



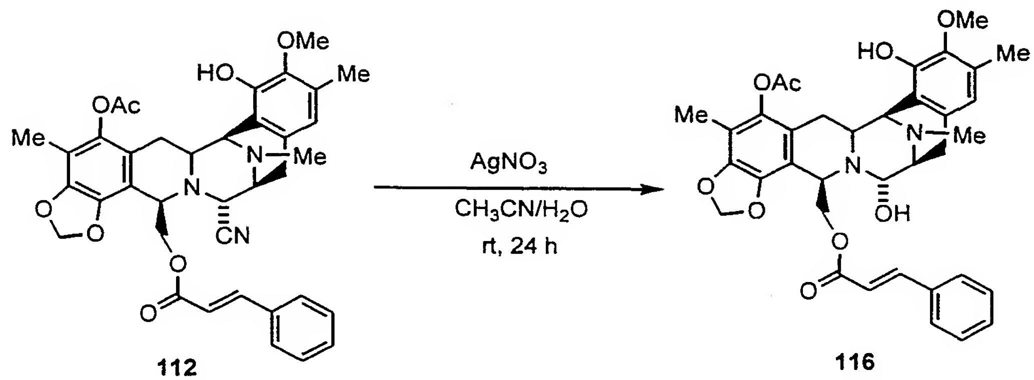
To a solution of **111** (12 mg, 0.018 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (93.5 mg, 0.55 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 1:1) to afford **115** (10 mg, 86 %) as a white solid.

Rf: 0.43 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.14 (m, 3H), 7.05-7.03 (m, 2H), 6.45 (s, 1H), 5.93 (d, J= 1.2 Hz, 1H), 5.88 (d, J= 1.2 Hz, 1H), 5.63 (brd, 1H), 4.55-4.49 (m, 2H), 4.43 (d, J= 2.7 Hz, 1H), 3.96 (d, J= 3.1 Hz, 1H), 3.80-3.73 (m, 1H), 3.56 (bs, 3H), 3.32 (dt, J_1= 3.3 Hz, J_2= 12.6 Hz, 1H), 3.13 (d, J= 6.0 Hz, 1H), 2.86 (dd, J_1= 7.5 Hz, J_2= 18.3 Hz, 1H), 2.74 (d, J= 14.7 Hz, 1H), 2.61-2.56 (m, 2H), 2.47 (d, J= 18.0 Hz, 1H), 2.33 (s, 3H), 2.23 (s, 3H), 2.13 (s, 3H), 2.01 (s, 3H), 1.99-1.94 (m, 2H), 1.78 (dd, J_1= 11.7 Hz, J_2= 15.0 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{36}H_{40}N_2O_9$: 644.7. Found $(M-17)^+$: 627.2.

Example 110



112 116

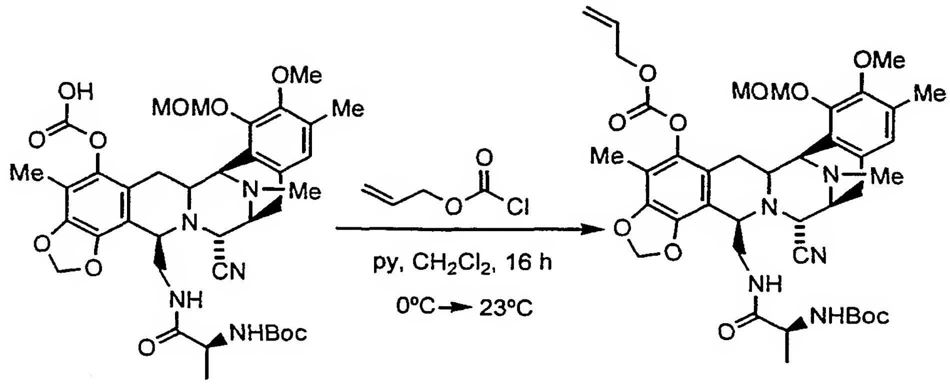
To a solution of **112** (12 mg, 0.018 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (93 mg, 0.55 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 1:1) to afford **116** (8 mg, 70 %) as a white solid.

Rf: 0.41 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.43 (m, 2H), 7.34-7.27 (m, 4H), 6.39 (s, 1H), 6.03 (d, *J*= 15.9 Hz, 1H), 5.96 (d, *J*= 1.5 Hz, 1H), 5.90 (d, *J*= 1.5 Hz, 1H), 5.55 (m, 1H), 4.47 (m, 1H), 4.50 (m, 1H), 3.94 (d, *J*= 3.6 Hz, 1H), 3.85 (dd, J_1= 3.3 Hz, J_2= 11.1 Hz, 1H), 3.66 (bs, 3H), 3.34-3.31 (m, 2H), 3.13 (d, *J*= 5.1 Hz, 1H), 2.93-2.73 (m, 2H), 2.53 (d, *J*= 18.0 Hz, 1H), 2.33 (s, 3H), 2.22 (s, 3H), 2.03 (s, 3H), 1.94-1.82 (m, 1H).

ESI-MS m/z: Calcd. for $C_{36}H_{38}N_2O_9$: 642.7. Found $(M-17)^+$: 625.2.

Example 111



17 117

To a solution of **17** (6.28 g, 9.06 mmol) in CH_2Cl_2 (45.3 mL), allyl chloroformiate (3.85 mL, 36.24 mmol) and pyridine (2.93 mL, 36.24 mmol) were added at 0 °C. The reaction mixture was stirred for 16 h at 23°C and then, the solution was diluted with CH_2Cl_2 (150 mL) and washed with 0.1 N HCl (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to give **117** (5.96 g, 84 %) which was used in following steps with no further purification.

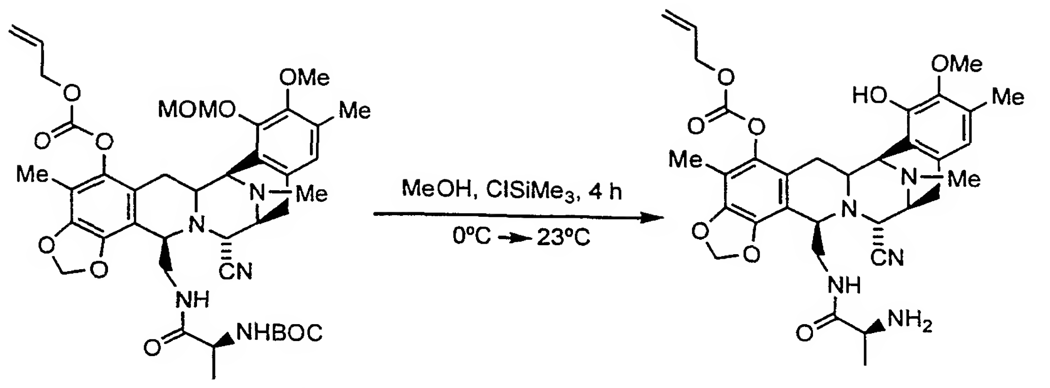
Rf: 0.56 (CH_2Cl_2:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 (s, 1H), 6.05-5.94 (m, 1H), 6.01 (s, 1H), 5.91 (s, 1H), 5.44 (dd, *J1* = 1.2 Hz, *J2* = 17.1 Hz, 1H), 5.35 (dd, *J1* = 1.2 Hz, *J2* = 10.5 Hz, 1H), 5.34 (m, 1H), 5.10 (d, *J* = 5.7 Hz, 1H), 5.05 (d, *J* = 5.7 Hz, 1H), 4.68 (d, *J* = 5.7 Hz, 1H), 4.65 (dt, *J1* = 1.2 Hz, *J2* = 6 Hz, 1H), 4.18 (brd, *J* = 9 Hz, 2H), 4.04 (bs, 1H), 3.70 (s, 3H), 3.67-3.60 (m, 1H), 3.55 (s, 3H), 3.43-3.41 (m, 2H), 3.29-3.25 (m, 2H), 3.00 (dd, *J1* = 8.7 Hz, *J2* = 18.3 Hz, 1H), 2.90 (dd, *J1* = 2.4 Hz, *J2* = 16.2 Hz, 1H), 2.75 (d, *J* = 18.3 Hz, 1H), 2.35 (s, 3H), 2.22 (s, 3H), 2.06 (s, 3H), 1.83 (dd, *J1* = 11.4 Hz, *J2* = 15.9 Hz, 1H), 1.39 (s, 9H). 0.73 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 152.8, 148.6, 148.3, 144.6, 140.7, 140.6, 131.5, 131.2, 131.1, 130.4, 125.3, 125.0, 123.3, 120.9, 119.1, 118.8, 117.6, 112.9, 112.0, 101.6, 99.2, 71.8, 69.0, 68.4, 59.7, 59.2, 57.6, 57.3, 56.7, 55.8, 55.2, 41.4, 39.9, 28.2, 26.0, 25.0, 18.6, 15.6, 9.0.

ESI-MS m/z: Calcd. for $C_{40}H_{51}N_5O_{11}$: 777.8. Found $(M+1)^+$: 778.3

Example 112



117 118

To a solution of **117** (3.96 g, 5.09 mmol) in MeOH (37.4 mL), trimetylchlorosilane (6.5 mL, 50.9 mmol) was added at 0 °C. The reaction mixture was stirred for 4 h at 23°C and then, the solvent was eliminated under reduced pressure. The residue was diluted with EtOAc (70 mL) and washed with a saturated aqueous solution of $NaHCO_2$ (2 x 45 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated *in vacuo* to give **118** (2.77 g, 86 %) which was used in following steps with no further purification.

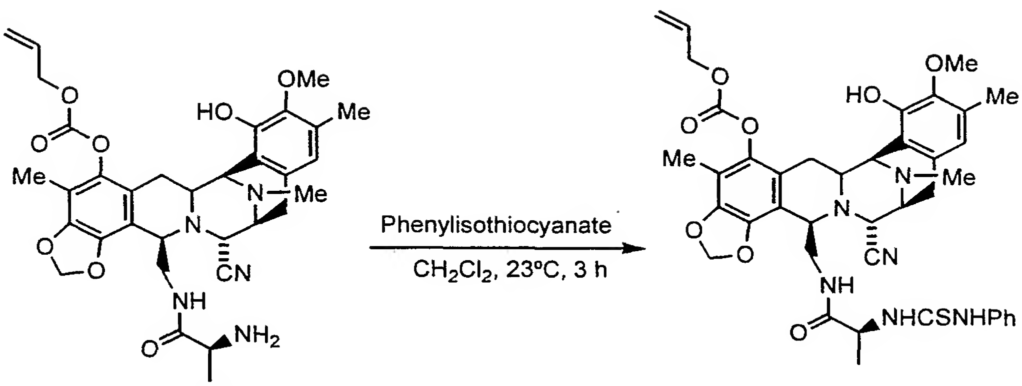
Rf: 0.61 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.45 (m, 1H), 6.10-6.03 (m, 1H), 6.00 (s, 1H), 5.93 (s, 1H), 5.47 (dd, $J1$ = 1.2 Hz, $J2$ = 17.1 Hz, 1H), 5.38 (dd, $J1$ = 1.2 Hz, $J2$ = 10.5 Hz, 1H), 4.81-4.64 (m, 2H), 4.10-4.03 (m, 3H), 3.75 (s, 3H), 3.70-3.44 (m, 2H), 3.35 (d, J = 8.1 Hz, 1H), 3.28 (dt, $J1$ = 2.7 Hz, $J2$ = 9 Hz, 1H), 2.98 (dd, $J1$ = 7.8 Hz, $J2$ = 18 Hz, 1H), 2.90 (dd, $J1$ = 2.7 Hz, $J2$ = 16.2 Hz, 1H), 2.78 (dd, $J1$ = 6.9 Hz, $J2$ = 14.1 Hz, 1H), 2.63 (d, J = 18.3 Hz, 1H), 2.30 (s, 3H), 2.25 (s, 3H), 2.04 (s, 3H), 1.88 (dd, $J1$ = 13.2 Hz, $J2$ = 15.6 Hz, 1H), 0.95 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 152.9, 146.6, 144.6, 142.5, 140.8, 140.6, 131.5, 131.3, 128.5, 121.1, 120.8, 118.9, 117.8, 117.0, 113.2, 111.9, 101.7, 68.9, 60.6, 59.1, 56.6, 56.4, 55.7, 55.2, 50.5, 41.7, 39.4, 26.1, 25.0, 21.0, 15.6, 9.2.

ESI-MS m/z: Calcd. for $C_{33}H_{39}N_5O_8$: 633.6. Found $(M+1)^+$: 634.2.

Example 113



118

119

To a solution of **118** (3.52 g, 5.56 mmol) in CH_2Cl_2 (28 mL), phenylisothiocyanate (3.99 mL, 33.36 mmol) was added at 23 °C. The reaction mixture was stirred for 3 and then, the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography to afford **119** (3.5 g, 82 %) as a white solid.

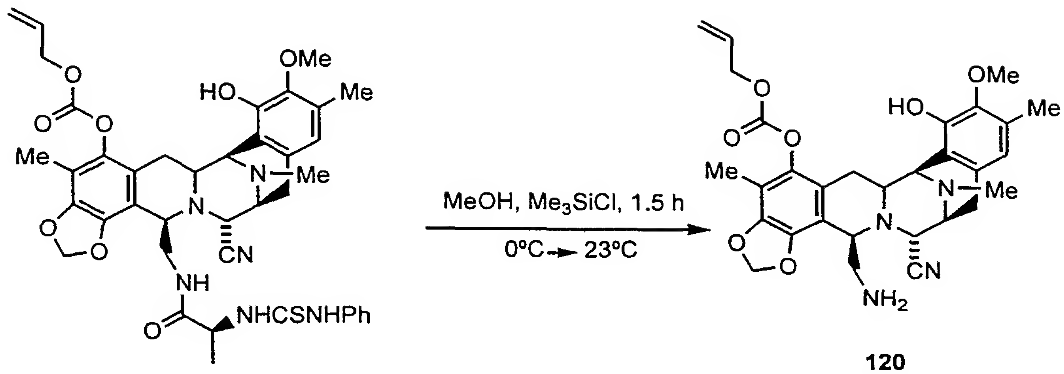
Rf: 0.52 (CH_2Cl_2:EtOAc 1:5).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69 (bs, 1H), 7.49-7.46 (m, 2H), 7.34-7.21 (m, 2H), 6.96 (d, J = 6.9 Hz, 1H), 6.06-5.97 (m, 1H), 6.03 (s, 1H), 5.96 (bs, 1H), 5.91 (s, 1H), 5.66 (s, 1H), 5.47 (dd, $J1$ = 1.5 Hz, $J2$ = 17.1 Hz, 1H), 5.37 (dd, $J1$ = 1.5 Hz, $J2$ = 10.5 Hz, 1H), 5.36 (s, 1H), 4.75-4.70 (m, 2H), 4.54-4-49 (m, 1H), 4.14 (d, J = 2.4 Hz, 1H), 4.07-4.06 (m, 2H), 3.70 (s, 3H), 3.44 (m, 1H), 3.35 (d, J = 8.1 Hz, 1H), 3.21 (dt, $J1$ = 2.7 Hz, $J2$ = 6.6 Hz, 1H), 2.94-2.82 (m, 2H), 2.63 (d, J = 18 Hz, 1H), 2.24 (s, 3H), 2.06 (s, 3H), 2.06 (s, 3H), 1.90 (dd, $J1$ = 11.7 Hz, $J2$ = 15.9 Hz, 1H), 0.71 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 178.6, 171.9, 152.8, 146.7, 144.5, 142.6, 140.8, 140.5, 136.3, 131.3, 131.0, 129.9, 129.8, 128.9, 126.7, 125.2, 124.3, 121.1, 120.6, 118.9, 117.7, 116.5, 112.8, 112.1, 101.6, 68.9, 60.5, 58.9, 57.3, 56.1, 55.9, 55.1, 53.3, 41.5, 39.2, 25.9, 24.6, 20.9, 15.4, 9.1.

ESI-MS m/z: Calcd. for $C_{40}H_{44}N_3O_8S$: 768.8. Found $(M+1)^+$: 769.3.

Example 114



119

120

To a solution of **119** (3.38 g, 4.4 mmol) in MeOH (22 mL), trimetylchlorosilane (2.3 mL, 22 mmol) was added at 0 °C. The reaction mixture was stirred for 1.5 h at 23°C and then, the solvent was eliminated under reduced pressure. The residue was diluted with EtOAc (100 mL) and washed with 0.1 N HCl (2 x 75 mL). The aqueous phase was basified with a saturated aqueous solution of $NaHCO_2$ and extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to afford **120** (2.47 g, 100 %) as a white solid which was used in following steps with no further purification.

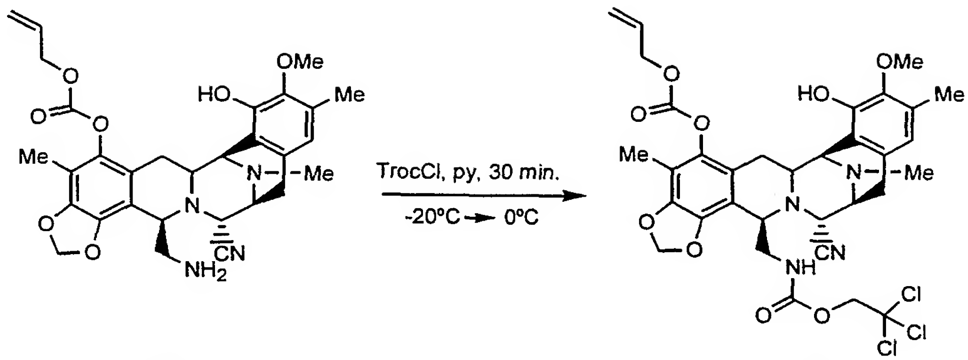
Rf: 0.26 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 1H), 6.05-5.98 (m, 1H), 5.97 (d, J = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 5.44 (dd, $J1$ = 1.2 Hz, $J2$ = 17.1 Hz, 1H), 5.35 (dd, $J1$ = 1.2 Hz, $J2$ = 10.2 Hz, 1H), 4.75-4.71 (m, 2H), 4.12-4.10 (m, 1H), 3.99 (d, J = 2.4 Hz, 1H), 3.92 (bs, 1H), 3.73 (s, 3H), 3.36-3.26 (m, 2H), 3.06 (dd, $J1$ = 8.4 Hz, $J2$ = 18 Hz, 1H), 2.89 (dd, $J1$ = 2.7 Hz, $J2$ = 15.9 Hz, 1H), 2.75-2.73 (m, 2H), 2.48 (d, J = 18 Hz, 1H), 2.32 (s, 3H), 2.23 (s, 3H), 2.05 (s, 3H), 1.85 (dd, $J1$ = 11.7 Hz, $J2$ = 15.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 153.0, 146.6, 144.5, 142.8, 140.7, 131.5, 130.5, 128.9, 121.3, 120.9, 119.1, 117.9, 116.7, 113.8. 111.6, 101.5, 69.0, 60.6, 59.8, 58.7, 56.5, 56.0, 55.3, 44.2, 41.8, 31.6, 26.1, 25.7, 15.7, 9.2.

ESI-MS m/z: Calcd. for $C_{30}H_{34}N_4O_7$: 562.6. Found $(M+1)^+$: 563. 2.

Example 115



120 121

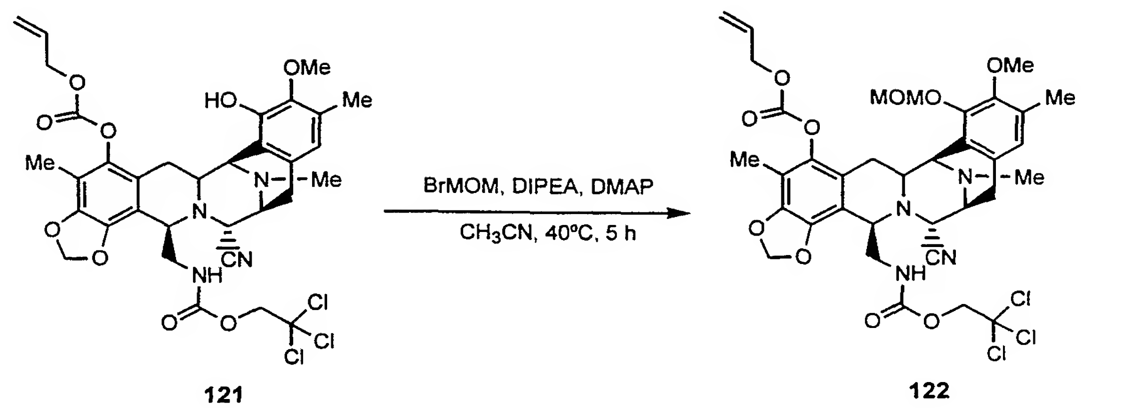
To a solution of **120** (2.57 g, 4.4 mmol) in CH_2Cl_2 (44 mL), TrocCl (0.91 mL, 6.6 mmol) and pyridine (0.53 mL, 6.6 mmol) were added at -20 °C. The reaction mixture was stirred for 30 min at 0°C and then, the solution was diluted with CH_2Cl_2 (50 mL) and washed with 0.1 N HCl (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to give **121** (3.24 g, 100 %) which was used in following steps with no further purification.

Rf: 0.62 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 6.07-6.01 (m, 1H), 5.99 (d, *J* = 1.2 Hz, 1H), 5.93 (d, *J* = 1.2 Hz, 1H), 5.68 (s, 1H), 5.46 (dd, *J1* = 1.2 Hz, *J2* = 17.1 Hz, 1H), 5.37 (dd, *J1* = 1.2 Hz, *J2* = 10.5 Hz, 1H), 4.74 (t, *J* = 5.7 Hz, 2H), 4.63-4.62 (m, 1H), 4.54 (d, *J* = 12 Hz, 1H), 4.30 (d, *J* = 12 Hz, 1H), 4.14-4.11 (m, 2H), 4.02-4.01 (m, 2H), 3.75 (s, 3H), 3.36-3.26 (m, 3H), 3.04 (dd, *J1* = 8.1 Hz, *J2* = 17.7 Hz, 1H), 2.91 (dd, *J1* = 2.4 Hz, *J2* = 15.6 Hz, 1H), 2.60 (d, *J* = 17.7Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 2.04 (s, 3H), 1.84 (dd, *J1* = 12 Hz, *J2* = 15.9 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{33}H_{35}Cl_3N_4O_9$: 738.0. Found $(M+1)^+$: 737.2.

Example 116



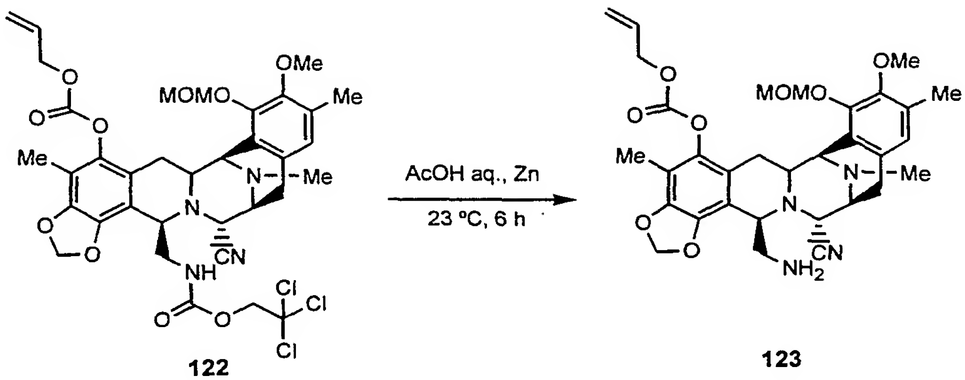
To a solution of **121** (0.45 g, 0.60 mmol) in CH_3CN (4 mL), diisopropylethylamine (2.17 mL, 12.46 mmol), bromomethyl methyl ether (0.76 mL, 9.34 mmol) and dimethylaminopyridine (8 mg, 0.062 mmol) were added at 0 °C. The reaction mixture was heated at 40°C for 5 h. Then, the reaction was diluted with CH_2Cl_2 (50 mL) and washed with 0.1 N HCl (2 x 25 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to give **122** (0.453 g, 95 %) which was used in following steps with no further purification.

Rf: 0.31 (RP-18 CH_3CN-H_2O 8:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.05-5.99 (m, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.43 (dd, $J1$ = 1.2 Hz, $J2$ = 17.1 Hz, 1H), 5.34 (dd, $J1$ = 1.2 Hz, $J2$ = 10.5 Hz, 1H), 5.10-5.04 (m, 2H), 4.72-4.68 (m, 2H), 4.60 (t, J = 5.7 Hz, 1H), 4.49 (d, J = 12.3 Hz, 1H), 4.38 (d, J = 12.3 Hz, 1H), 4.18 (d, J = 2.7 Hz, 1H), 4.03-4.00 (m, 2H), 3.71 (s, 3H), 3.54 (s, 3H), 3.38-3.22 (m, 4H), 3.04 (dd, $J1$ = 7.8 Hz, $J2$ = 18.3 Hz, 1H), 2.91 (dd, $J1$ = 2.4 Hz, $J2$ = 15.9 Hz, 1H), 2.61 (d, J = 18 Hz, 1H), 2.31 (s, 3H), 2.20 (s, 3H), 2.03 (s, 3H), 1.76 (dd, $J1$ = 11.7 Hz, $J2$ = 15.6 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{33}H_{39}Cl_3N_4O_{10}$: 782.0. Found $(M+1)^+$: 783.2.

Example 117



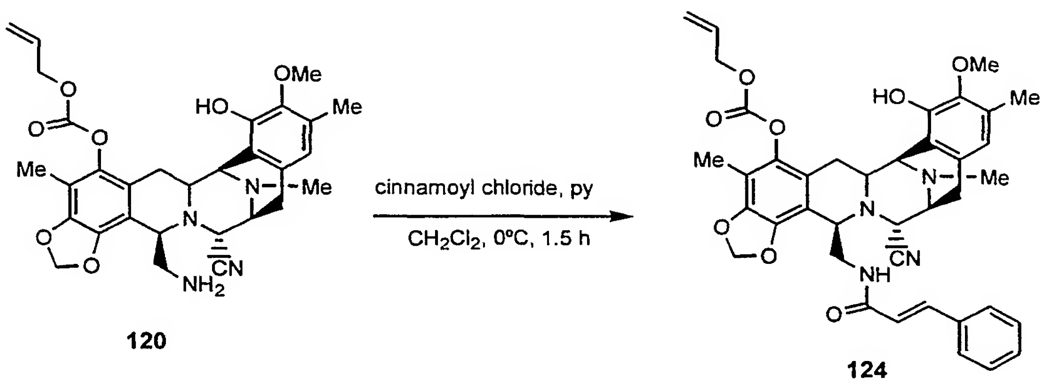
To a suspension of **122** (0.45 g, 0.579 mmol) in 90 % aqueous acetic acid (6 mL), powder zinc (0.283 g, 4.34 mmol) was added and the reaction was stirred for 6 h at 23 °C. Then, the mixture was filtered through a pad of celite which was washed with CH_2Cl_2 (25 mL). The organic layer was washed with an aqueous sat. solution of sodium bicarbonate (pH= 9) (2 x 15 mL), dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to give **123** (0.351 g, 100 %) which was used in following steps with no further purification.

Rf: 0.38 (SiO_2, EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68 (s, 1H), 6.06-5.99 (m, 1H), 5.97 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.25 Hz, 1H), 5.44 (dd, $J1$ = 1.5 Hz, $J2$ = 17.4 Hz, 1H), 5.36 (dd, $J1$ = 1.5 Hz, $J2$ = 10.2 Hz, 1H), 5.08 (q, J = 5.7 Hz, 2H), 5.74-4.70 (m, 2H), 4.02 (d, J = 3 Hz, 1H), 4.00 (d, J = 2.4 Hz, 1H), 3.91 (m, 1H), 3.71 (s, 3H), 3.56 (s, 3H), 3.37-3.35 (m, 1H), 3.29 (t, J = 2.7 Hz, 1H), 3.08 (dd, $J1$ = 7.5 Hz, $J2$ = 18 Hz, 1H), 2.90 (dd, $J1$ = 2.7 Hz, $J2$ = 15.9 Hz, 1H), 2.74 (dd, $J1$ = 2.4 Hz, $J2$ = 5.1 Hz, 2H), 2.48 (d, J = 18 Hz, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 2.05 (s, 3H), 1.80 (dd, $J1$ = 12 Hz, $J2$ = 15.9 Hz, 2H).

ESI-MS m/z: Calcd. for $C_{32}H_{38}N_4O_8$: 606.6. Found $(M+1)^+$: 607.3.

Example 118



To a solution of **120** (100 mg, 0.177 mmol) in CH_2Cl_2 (0.7 mL), cinnamoyl chloride (29.5 mg, 0.177 mmol) and pyridine (14.37 μL, 0.177 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 2:1 to Hex:EtOAc 1:3) to afford **124** (86 mg, 70 %) as a white solid.

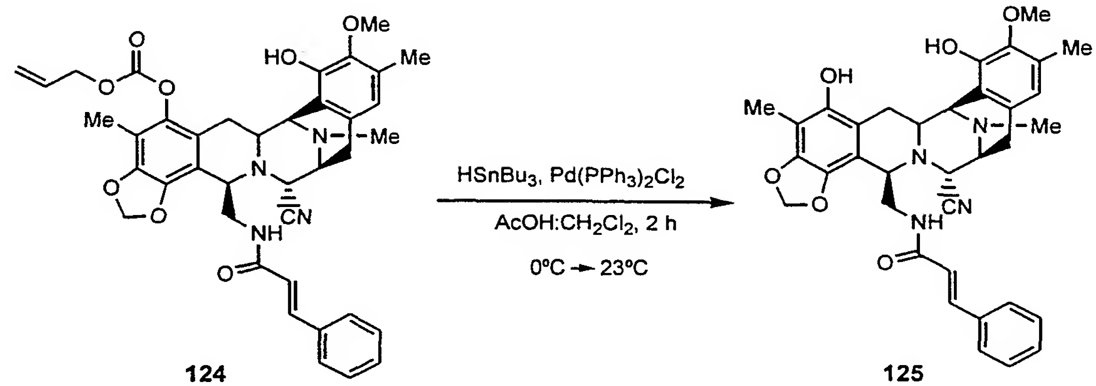
Rf: 0.77 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 7.25 (d, J = 15.6 Hz, 1H), 6.44 (s, 1H), 6.01 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 5.68 (s, 1H), 5.65 (d, J = 15.6 Hz, 1H), 5.44 (dd, J1 = 1.2 Hz, J2 = 17.1 Hz, 1H), 5.35 (dd, J1 = 1.2 Hz, J2 = 10.5 Hz, 1H), 5.18 (t, J = 6 Hz, 1H), 4.73-4.69 (m, 2H), 4.11-4.09 (m, 3H), 3.66-3.58 (m, 2H), 3.65 (s, 3H), 3.38-3.31 (m, 3H), 3.02 (dd, J1 = 8.4 Hz, J2 = 18.3 Hz, 1H), 2.92 (dd, J1 = 2.7 Hz, J2 = 15.6 Hz, 1H), 2.59 (d, J = 18.3 Hz, 1H), 2.31 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.89 (dd, J1 = 12.3 Hz, J2 = 16.2 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 152.7, 146.6, 144.4, 142.6, 140.7, 140.5, 140.1, 134.7, 131.2, 130.6, 129.3, 128.7, 128.4, 127.6, 120.8, 120.5, 120.3, 118.9, 117.6, 116.5, 113.2, 111.8, 101.6, 68.8, 60.4, 59.0, 56.2, 56.1, 55.7, 55.0, 41.5, 40.6, 25.9, 25.1, 15.5, 9.0.

ESI-MS m/z: Calcd. for $C_{39}H_{40}N_4O_8$: 692.7. Found $(M+1)^+$: 693.2.

Example 119



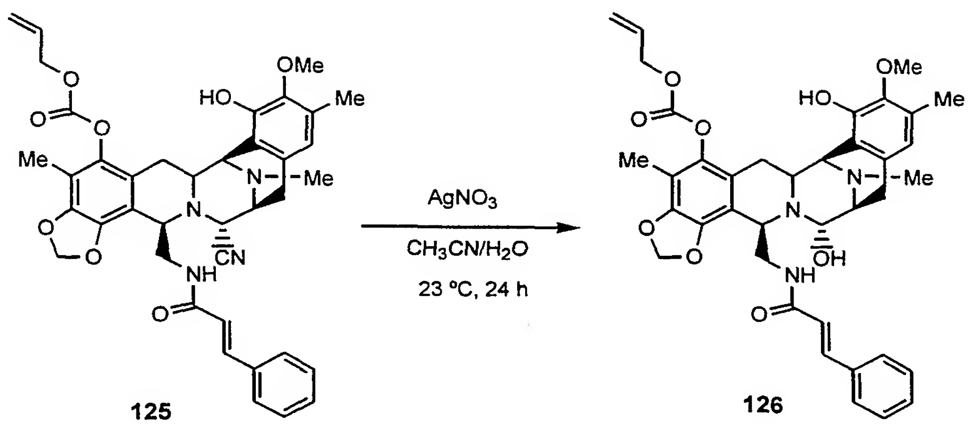
To a solution of **124** (495 mg, 0.713 mmol) in CH_2Cl_2 (28 mL), acetic acid (163 μL), $Pd(PPh_3)_2Cl_2$ (50 mg, 0.0713 mmol) and Bu_3SnH (384 μL, 1.42 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h at 23°C and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 1:1 to EtOAc) to afford **125** (435 mg, 100 %) as a white solid. Rf: 0.22 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H), 7.28 (d, J = 15.9 Hz, 1H), 6.45 (s, 1H), 5.90 (s, 1H), 5.83 (s, 1H), 5.55 (d, J = 15.6 Hz, 1H), 5.24 (t, J = 12.9 Hz, 1H), 4.17 (d, J = 1.8 Hz, 1H), 4.10-4.07 (m, 2H), 3.72 (s, 3H), 3.46-3.32 (m, 3H), 3.14-3.00 (m, 2H), 2.54 (d, J = 18 Hz, 1H), 2.32 (s, 3H), 2.05 (s, 6H), 1.89 (dd, J_1 = 12 Hz, $J2$ = 15.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 146.9, 145.1, 144.2, 143.0, 140.8, 136.5, 134.5, 130.6, 129.4, 128.9, 127.9, 127.7, 120.8, 119.8, 117.8, 114.1, 112.9, 107.1, 100.8, 60.5, 59.2, 56.4, 56.0, 55.1, 41.4, 30.7, 25.5, 25.3, 15.5, 8.9.

ESI-MS m/z: Calcd. for $C_{35}H_{36}N_4O_6$: 608. 6. Found $(M+1)^+$: 609.2.

Example 120



To a solution of **125** (86 mg, 0.124 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (632 mg, 3.72 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 2:1) to afford **126** (70 mg, 83 %) as a white solid.

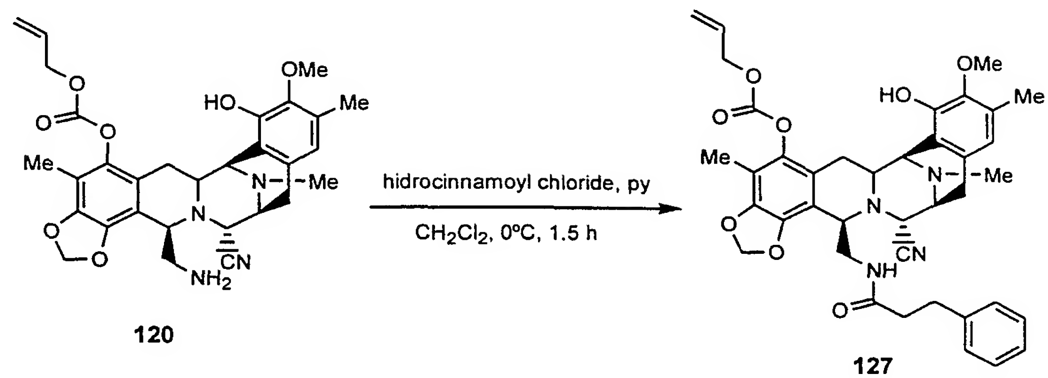
Rf: 0.07 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 7.25 (d, J = 15.6 Hz, 1H), 6.48 (s, 1H), 6.00-5.94 (m, 1H), 5.96 (s, 1H), 5.92 (s, 1H), 5.89 (s, 1H), 5.53 (d, J = 15.6 Hz, 1H), 5.42-5.36 (m, 2H), 5.31 (dd, J_1 = 1.2 Hz, $J2$ = 10.8 Hz, 1H), 4.71-4.65 (m, 2H), 4.51 (d, J = 3 Hz, 1H), 4.42 (bs, 1H), 4.07 (bs, 1H), 3.79 (dd, J_1 = 6.9 Hz, $J2$ = 12.9 Hz, 1H), 3.68 (s, 3H), 3.62-3.59 (m, 1H), 3.41-3.37 (m, 1H), 3.16 (d, J = 7.8 Hz, 1H), 2.95 (dd, J_1 = 7.5 Hz, $J2$ = 17.4 Hz, 1H), 2.88-2.83 (m, 1H), 2.43 (d, J = 18 Hz, 1H), 2.28 (s, 3H), 2.10 (s, 3H), 2.00 (s, 3H), 1.81 (dd, J_1 = 11.7 Hz, $J2$ = 15.3 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 165.5, 152.9, 146.7, 144.5, 144.4, 142.7, 141.0, 140.0, 134.6, 131.4, 130.7, 129.2, 128.8, 128.5, 127.8, 127.7, 124.6, 121.2, 120.9, 118.9, 116.5, 114.9, 114.7, 111.3, 101.6, 93.3, 92.3, 83.2, 68.9, 60.6, 57.8, 56.8, 56.6, 56.3, 52.5, 52.2, 41.6, 26.1, 24.6, 15.6, 9.1.

ESI-MS m/z: Calcd. for $C_{38}H_{41}N_3O_9$: 683.7. Found $(M-17)^+$: 666.3

Example 121



To a solution of **120** (1.61 g, 2.85 mmol) in CH_2Cl_2 (4 mL), hydrocinnamoyl chloride (423 µL, 2.85 mmol) and pyridine (230 µL, 2.85 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (50 mL) and washed with 0.1 N HCl (30 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 2:1 to EtOAc) to afford **127** (1.64 g, 83 %) as a white solid.

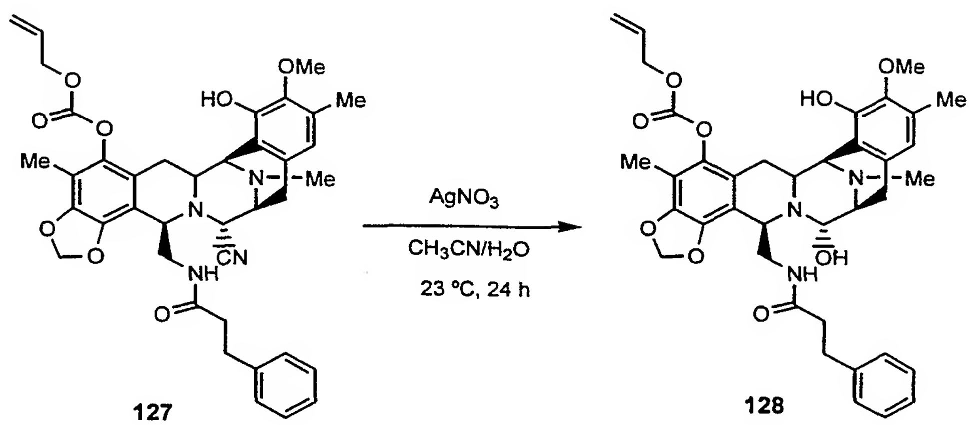
Rf: 0.63 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7-14 (m, 3H), 7.04-7.01 (m, 2H), 6.44 (s, 1H), 6.07-5.99 (m, 1H), 5.97 (d, J = 1.5 Hz, 1H), 5.91 (d, J = 1.5 Hz, 1H), 5.75 (bs, 1H), 5.45 (dd, J_1 = 1.5 Hz, $J2$ = 17.4 Hz, 1H), 5.36 (dd, J_1 = 1.5 Hz, $J2$ = 10.2 Hz, 1H), 5.03 (t, J = 5.7 Hz, 1H), 5.74-5.66 (m, 2H), 4.09 (d, J = 2.4 Hz, 1H), 4.01 (bs, 1H), 3.97 (d, J = 2.7 Hz, 1H), 3.62 (dd, J_1 = 8.4 Hz, $J2$ = 13.5 Hz, 1H), 3.42 (s, 3H), 3.37-3.28 (m, 3H), 3.04-2.87 (m, 3H), 2.67-2.46 (m, 4H), 2.29 (s, 3H), 2.05 (s, 3H), 2.03 (s, 3H), 1.83-1.79 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 152.8, 146.7, 144.5, 144.4, 142.7, 140.9, 140.8, 140.6, 131.4, 130.7, 128.9, 128.4, 128.2, 128.1, 126.0, 120.8, 120.4, 118.9, 117.6, 116.6, 113.0, 111.9, 101.6, 68.9, 60.3, 59.0, 56.3, 56.2, 55.6, 55.1, 41.6, 40.3, 37.7, 31.0, 25.9, 25.2, 15.5, 9.1.

ESI-MS m/z: Calcd. for $C_{39}H_{42}N_4O_8$: 694.3. Found $(M+1)^+$: 695.3.

Example 122



127 128

To a solution of **127** (50 mg, 0.072 mmol) in CH_3CN/H_2O (1.5 mL/1 mL), $AgNO_3$ (444 mg, 2.16 mmol) was added and the reaction was stirred at 23 °C for 24 h. Then, brine (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0 °C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (15 mL). The solution was extracted and the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAc:MeOH 3:1) to afford **128** (30 mg, 61 %) as a white solid.

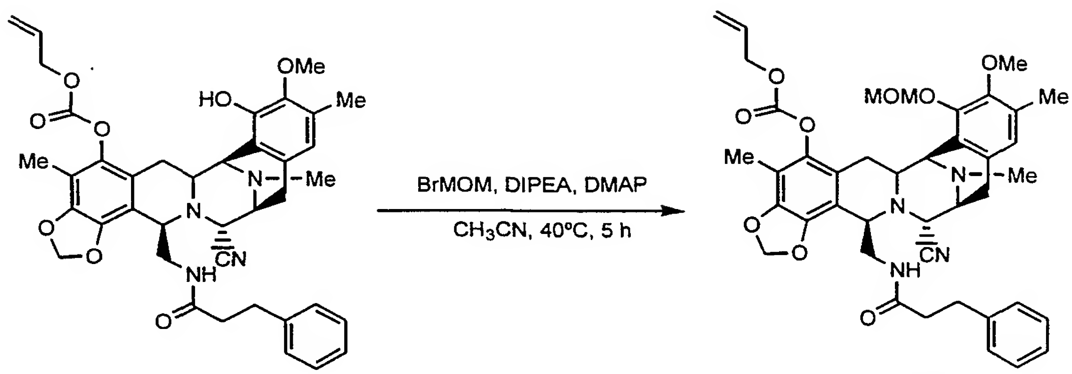
Rf: 0.65 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22-7.11 (m, 3H), 7.06-7.03 (m, 2H), 6.43 (s, 1H), 6.08-5.98 (m, 1H), 5.96 (d, J = 1.5 Hz, 1H), 5.90 (d, J = 1.5 Hz, 1H), 5.66 (bs, 1H), 5.44 (dd, J_1 = 1.5 Hz, $J2$ = 17.4 Hz, 1H), 5.36 (dd, J_1 = 1.5 Hz, $J2$ = 10.5 Hz, 1H), 4.78-4.65 (m, 2H), 4.44 (d, J = 3 Hz, 1H), 4.36 (bs, 1H), 3.99 (td, $J1$ = 2.1 Hz, $J2$ = 9.9 Hz, 1H), 3.78-3.67 (m, 1H), 3.56 (dt, $J1$ = 1.5 Hz, $J2$ = 11.1 Hz, 1H), 3.43 (s, 3H), 3.30-3.12 (m, 2H), 3.02-2.89 (m, 1H), 2.83 (dd, $J1$ = 2.7 Hz, $J2$ = 15.9 Hz, 1H), 2.62-2.51 (m, 2H), 2.36 (d, J = 18.6 Hz, 1H), 2.27 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.86-1.66 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 146.7, 141.2, 141.1, 131.5, 130.5, 128.9, 128.3, 128.2, 128.2, 125.9, 124.7, 121.1, 121.0, 118.8, 111.3, 101.6, 94.0, 83.2, 68.8, 60.3, 57.9, 56.6, 56.3, 52.3, 52.0, 41.7, 41.6, 41.1, 37.9, 31.1, 31.0, 26.1, 24.6, 15.5, 9.2. .

ESI-MS m/z: Calcd. for $C_{38}H_{43}N_3O_9$: 685.7. Found $(M-17)^+$: 668.3.

Example 123



To a solution of **127** (1.64 g, 2.36 mmol) in CH_3CN (12 mL), diisopropylethylamine (8.22 mL, 47.2 mmol), bromomethyl methyl ether (2.89 mL, 35.4 mmol) and dimethylaminopyridine (29 mg, 0.236 mmol) were added at 0 °C. The reaction mixture was heated at 40°C for 5 h. Then, the reaction was diluted with CH_2Cl_2 (80 mL) and washed with 0.1 N HCl (3 x 25 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure to give **129** (1.46 g, 84 %) which was used in following steps with no further purification.

Rf: 0.24 (RP-18 CH_3CN-H_2O 8:2).

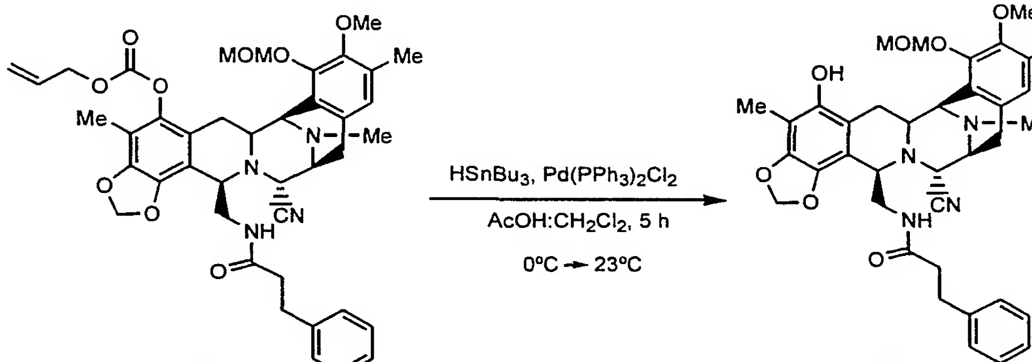
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.11 (m, 3H), 7.05-7.02 (m, 2H), 6.67 (s, 1H), 6.08-5.98 (m, 1H), 5.96 (d, J = 1.2 Hz, 1H), 5.90 (d, J = 1.2 Hz, 1H), 5.44 (dd, $J1$ = 1.2 Hz, $J2$ = 17.1Hz, 1H), 5.34 (dd, $J1$ = 1.2 Hz, $J2$ = 10.5 Hz, 1H), 5.05 (d, J = 6 Hz, 1H), 5.00 (d, J = 6 Hz, 1H), 4.97 (t, J = 5.1 Hz, 1H), 4.75-4.68 (m, 2H), 4.16 (d, J = 2.7 Hz, 1H), 3.98-3.97 (m, 1H), 3.68-3.67 (m, 1H), 3.65-3.61 (m, 1H), 3.52 (s, 3H), 3.35 (s, 3H), 3.32-3.26 (m, 3H), 3.05-2.86 (m, 3H), 2.59-2.48 (m, 2H), 2.30 (s, 3H), 2.02 (s, 3H), 1.94 (s, 3H), 1.91-1.67 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 152.7, 148.5, 148.3, 144.5, 140.9, 140.8, 140.4, 131.1, 130.9, 130.4, 130.1, 128.4, 128.2, 126.0, 124.6, 123.7, 120.3, 119.0, 112.9, 111.8, 101.6, 99.1, 68.9, 59.4, 59.1, 57.5, 56.7, 56.3, 55.4, 55.1, 41.5, 40.2, 37.7, 30.9, 25.8, 25.2, 15.5,

9.0.

ESI-MS m/z: Calcd. for $C_{41}H_{46}N_4O_9$: 738.8. Found $(M+23)^+$: 761.2.

Example 124



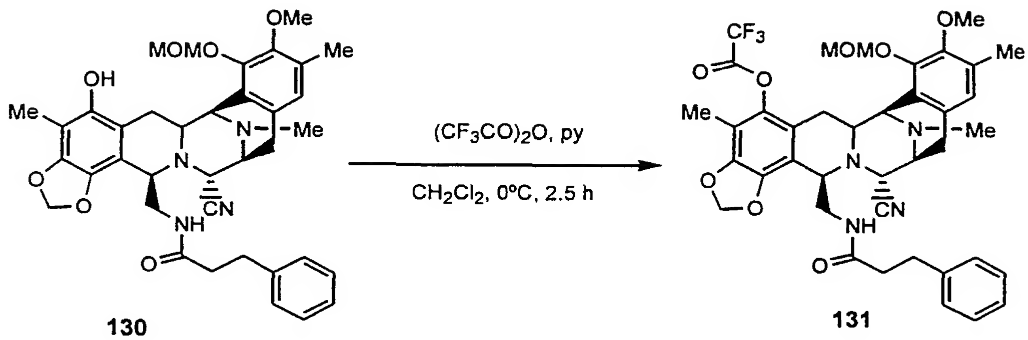
To a solution of **129** (1.46 g, 1.97 mmol) in CH_2Cl_2 (40 mL), acetic acid (450 μL), $Pd(PPh_3)_2Cl_2$ (138 mg, 0.197 mmol) and Bu_3SnH (1.06 mL, 3.95 mmol) were added at 0 °C. The reaction mixture was stirred for 5 h at 23°C and then, the solution was poured into a pad of flash column (SiO_2, gradient Hex:EtOAc 1:1 to EtOAc) to afford **130** (1.1 g, 85 %) as a white solid. Rf: 0.22 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.12 (m, 3H), 6.98-6.95 (m, 2H), 5.86 (s, 1H), 5.84 (s, 1H), 5.79 (bs, 1H), 5.26 (d, J = 6 Hz, 1H), 5.11 (d, J = 6 Hz, 1H), 5.05 (t, J = 5.7 Hz, 1H), 4.19 (d, J = 2.4 Hz, 1H), 4.03 (d, J = 2.4 Hz, 1H), 3.99 (bs, 1H), 3.65 (s, 3H), 3.56 (s, 3H), 3.53-3.42 (m, 2H), 3.34 (d, J = 8.7 Hz, 1H), 3.27 (brd, J = 11.7 Hz, 1H), 3.11 (d, J = 15 Hz, 1H), 2.99 (dd, $J1$ = 8.4 Hz, $J2$ = 18.3 Hz, 1H), 2.64-2.52 (m, 3H), 2.29 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.84 (t, J = 7.8 Hz, 2H), 1.71 (dd, $J1$ = 12.9 Hz, $J2$ = 13.5 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 149.0, 147.6, 140.6, 132.1, 131.9, 130.9, 130.5, 128.5, 128.4, 128.3, 128.0, 126.0, 124.9, 124.6, 123.1, 117.6, 100.8, 99.6, 59.6, 58.9, 57.6, 56.6, 56.5, 55.6, 55.1, 41.5, 37.8, 31.5, 31.1, 25.9, 25.1, 22.6, 15.5, 8.8.

ESI-MS m/z: Calcd. for $C_{37}H_{42}N_4O_7$: 654.7. Found (M^++ Na): 655.1

Example 125



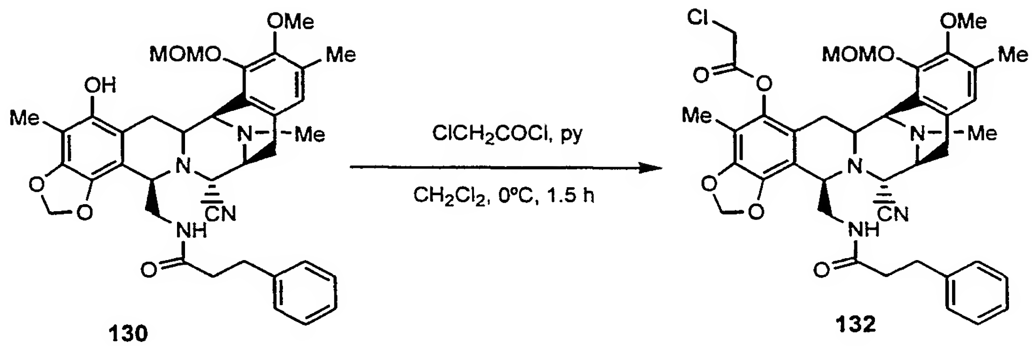
To a solution of **130** (130 mg, 0.198 mmol) in CH_2Cl_2 (1 mL), trifluoroacetyl anhydride (41.9 μL, 0.297 mmol) and pyridine (24 μL, 0.297 mmol) were added at 0 °C. The reaction mixture was stirred for 2.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 4:1 to Hex:EtOAc 1:4) to afford **131** (93 mg, 62 %) as a white solid.

Rf: 0.30 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.16 (m, 3H), 7.04-7.02 (m, 2H), 6.78 (s, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.95 (d, J = 1.2 Hz, 1H), 5.11 (d, J = 6.6 Hz, 1H), 4.98 (d, J = 6.6 Hz, 1H), 4.95 (t, J = 6.3 Hz, 1H), 4.61 (bs, 1H), 4.30 (s, 1H), 4.08 (s, 1H), 3.96 (d, J = 7.2 Hz, 1H), 3.66-3.54 (m, 1H), 3.50 (s, 3H), 3.39 (s, 3H), 3.19 (dd, J1 = 7.8 Hz, J2 = 18.3 Hz, 1H), 2.88 (d, J = 18.6 Hz, 1H), 2.79 (dd, J1 = 2.7 Hz, J2 = 15.9 Hz, 1H), 2.66-2.62 (m, 1H), 2.57 (s, 3H), 2.06 (s, 6H), 1.94-1.87 (m, 1H), 1.77-1.68 (m, 2H).

ESI-MS m/z: Calcd. for $C_{39}H_{41}F_3N_4O_8$: 750.7. Found $(M+Na)^+$: 751.2.

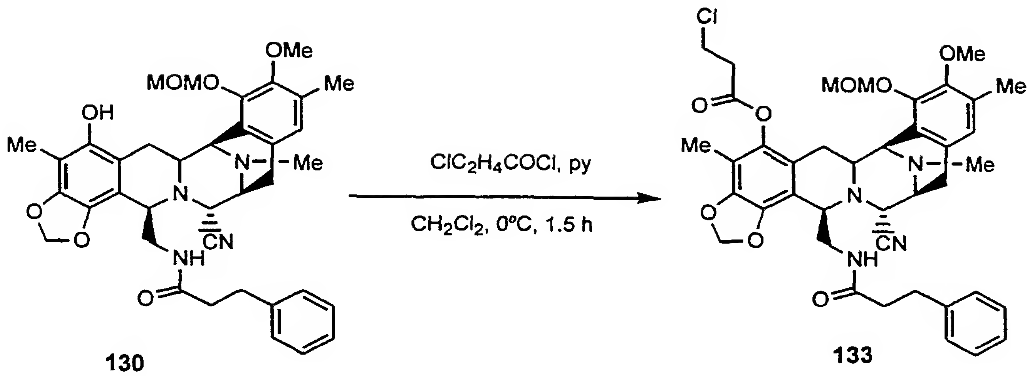
Example 126



To a solution of **130** (130 mg, 0.198 mmol) in CH_2Cl_2 (2 mL), chloroacetyl chloride (23.65 μL, 0.297 mmol) and pyridine (24 μL, 0.297 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 2:1 to Hex:EtOAc 1:1) to afford **132** (130 mg, 90 %) as a white solid.

Rf: 0.31 (Hex:EtOAc 1:2).
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (m, 3H), 7.07-7.05 (m, 2H), 6.69 (s, 1H), 6.00 (d, J = 1.5 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.11 (d, J = 5.7 Hz, 1H), 5.04 (d, J = 5.7 Hz, 1H), 4.93 (m, 1H), 4.36 (s, 2H), 4.16 (d, J = 2.7 Hz, 1H), 4.01 (m, 2H), 3.64 (dd, $J1$ = 6.9 Hz, $J2$ = 12.3 Hz, 1H), 3.54 (s, 3H), 3.40 (s, 3H), 3.38-3.35 (m, 2H), 2.29 (dt, $J1$ = 3 Hz, $J2$ = 12 Hz, 1H), 3.03 (dd, $J1$ = 7.8 Hz, $J2$ = 18 Hz, 1H), 2.77 (dd, $J1$ = 2.4 Hz, $J2$ = 16.2 Hz, 1H), 2.58-2.52 (m, 3H), 2.32 (s, 3H), 2.02 (s, 3H), 1.92-1.85 (m, 1H), 1.76-1.65 (m, 2H).
^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 164.9, 148.3, 144.6, 140.9, 140.8, 139.8, 132.1, 131.9, 131.1, 130.0, 128.2, 126.0, 125.0, 124.6, 123.5, 120.1, 117.5, 113.0, 111.5, 101.7, 99.1, 64.9, 59.7, 58.9, 57.7, 56.6, 56.4, 55.2, 55.1, 41.5, 40.2, 39.9, 37.7, 30.9, 26.3, 25.1, 15.4, 9.1.
ESI-MS m/z: Calcd. for $C_{39}H_{43}ClN_4O_8$: 730.2. Found $(M+1)^+$: 731.1.

Example 127



To a solution of **130** (130 mg, 0.198 mmol) in CH_2Cl_2 (2 mL), chloropropionyl chloride (28.35 μL, 0.297 mmol) and pyridine (24 μL, 0.297 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (10 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 1:1) to afford **133** (94 mg, 64 %) as a white solid.

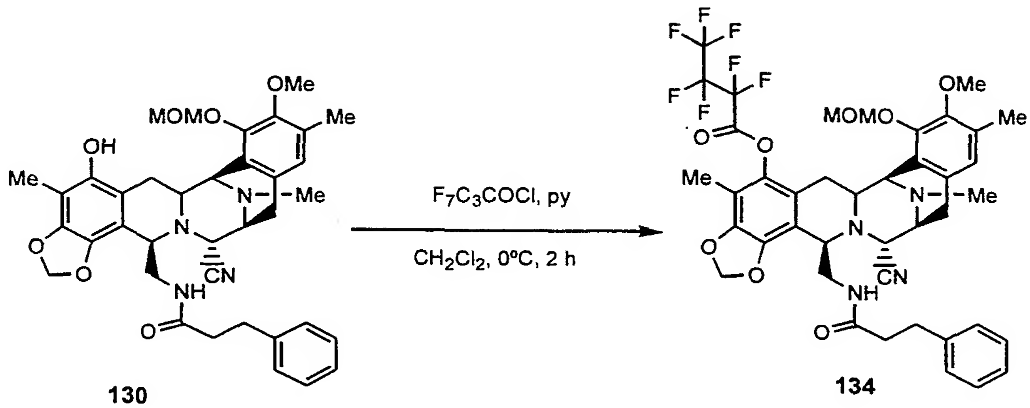
Rf: 0.43 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.12 (m, 3H), 7.06-7.04 (m, 2H), 6.69 (s, 1H), 5.97 (s, 1H), 5.92 (s, 1H), 5.08 (d, J = 6 Hz, 1H), 5.00 (d, J = 6 Hz, 1H), 4.97 (m, 1H), 4.16 (bs, 1H), 4.00 (m, 1H), 3.88 (t, J = 6.9 Hz, 2H), 3.75 (t, J = 6.9 Hz, 2H), 3.59 (dd, $J1$ = 6.3 Hz, $J2$ = 12.3 Hz, 1H), 3.53 (s, 3H), 3.37 (s, 3H), 3.03-3.26 (m, 1H), 3.17-2.97 (m, 3H), 2.83-2.73 (m, 2H), 2.58-2.52 (m, 3H), 2.31 (s, 3H), 2.03 (s, 6H), 1.93-1.86 (m, 1H), 1.79-1.64 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 167.8, 148.3, 144.7, 140.8, 132.1, 132.0, 131.1, 130.2, 128.2, 126.1, 125.2, 124.6, 123.7, 122.2, 120.2, 117.6, 114.7, 112.9, 111.8, 101.7, 99.3, 74.9, 65.0, 59.6, 59.0, 57.7, 56.7, 56.4, 55.4, 55.1, 41.5, 38.5, 37.8, 37.2, 31.0, 26.4, 25.2, 15.5, 9.3.

ESI-MS m/z: Calcd. for $C_{40}H_{45}ClN_4O_8$: 744.2. Found $(M+1)^+$: 745.0.

Example 128



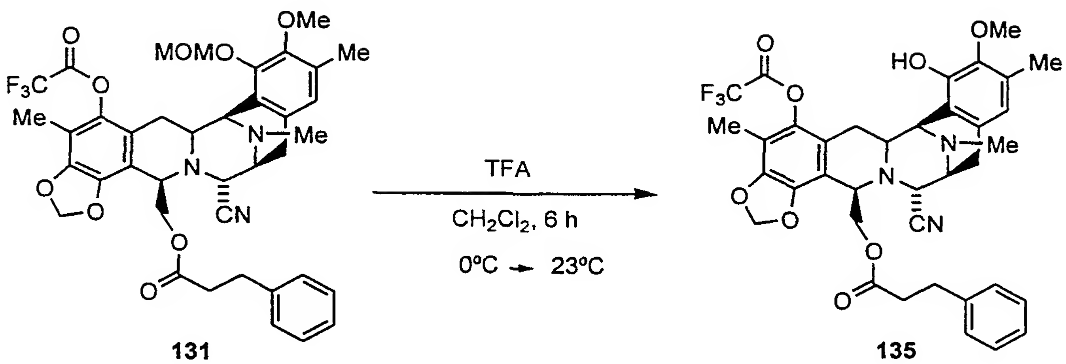
To a solution of **130** (160 mg, 0.244 mmol) in CH_2Cl_2 (2 mL), heptafluorobutyryl chloride (54.5 µL, 0.366 mmol) and pyridine (40 µL, 0.49 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (10 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 2:1 to Hex:EtOAc 1:4) to afford **134** (120 mg, 63 %) as a white solid.

Rf: 0.40 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.16 (m, 3H), 7.04-7.02 (m, 2H), 6.77 (s, 1H), 6.02 (d, J = 1.5 Hz, 1H), 5.96 (d, J = 1.5 Hz, 1H), 5.11 (d, J = 6.6 Hz, 1H), 4.95 (d, J = 6.6 Hz, 1H), 4.94 (m, 1H), 4.58 (m, 1H), 4.25 (bs, 1H), 4.06 (bs, 1H), 3.88 (d, J = 6.9 Hz, 1H), 3.64 (dd, $J1$ = 7.5 Hz, $J2$ = 12.9 Hz, 1H), 3.55-3.53 (m, 1H), 3.49 (s, 3H), 3.38 (s, 3H), 3.17 (dd, $J1$ = 8.1 Hz, $J2$ = 18.9 Hz, 1H), 2.85 (d, J = 18.3 Hz, 1H), 2.77 (dd, $J1$ = 2.7 Hz, $J2$ = 16.2 Hz, 1H), 2.60-2.57 (m, 3H), 2.56 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.96-1.88 (m, 1H), 1.79-1.69 (m, 2H).

ESI-MS m/z: Calcd. for $C_{41}H_{41}F_7N_4O_8$: 850.7. Found $(M+1)^+$: 851.3.

Example 129

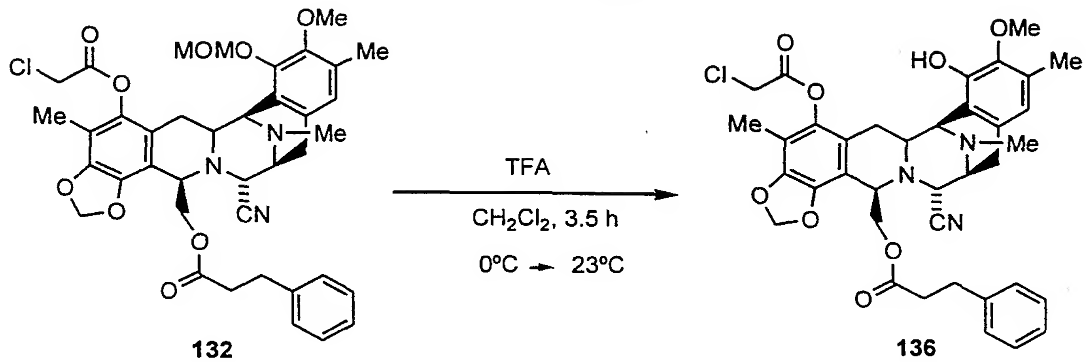


To a solution of **131** (93 mg, 0.123 mmol) in CH_2Cl_2 (1 mL), trifluoroacetic acid (381 µL, 4.95 mmol) was added at 0 °C and the reaction mixture was stirred for 6 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to give **135** (65 mg, 75 %) as a white solid which was used in following steps with no further purification. Rf: 0.26 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 - 7.15 (m, 3H), 7.04 - 7.01 (m, 2H), 6.45 (s, 1H), 6.03 (d, *J* = 1.5 Hz, 1H), 5.97 (d, *J* = 1.5 Hz, 1H), 5.62 (s, 1H), 4.97 (m, 1H), 4.09 (d, *J* = 1.8 Hz, 1H), 4.03 (bs, 1H), 3.99 (d, *J* = 2.4 Hz, 1H), 3.73 (dd, J1= 7.5 Hz, *J2* = 12 Hz, 1H), 3.38 (s, 3H), 3.34 - 3.28 (m, 3H), 3.05 (dd, J1= 8.4 Hz, *J2* = 18.3 Hz, 1H), 2.75 (dd, J1= 3.3 Hz, *J2* = 16.5 Hz, 1H), 2.60 - 2.47 (m, 3H), 2.30 (s, 3H), 2.05 (s, 3H), 2.02 (s, 3H), 1.91 - 1.65 (m, 3H).

ESI-MS m/z: Calcd. for $C_{37}H_{37}F_3N_4O_7$: 706.2. Found $(M+1)^+$: 707.2.

Example 130



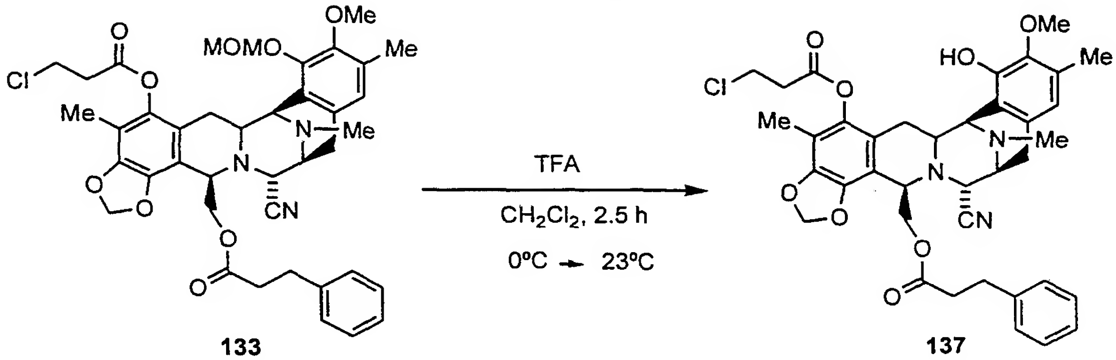
To a solution of **132** (130 mg, 0.177 mmol) in CH_2Cl_2 (1 mL), trifluoroacetic acid (545 μL, 7.08 mmol) was added at 0 °C and the reaction mixture was stirred for 3.5 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to give **136** (118 mg, 97 %) as a white solid which was used in following steps with no further purification. Rf: 0.27 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 - 7.13 (m, 3H), 7.06 - 7.03 (m, 2H), 6.45 (s, 1H), 5.98 (d, *J* = 1.2 Hz, 1H), 5.91 (d, *J* = 1.2 Hz, 1H), 5.04 (t, *J* = 4.5 Hz, 1H), 4.37 (bs, 2H), 4.13 (d, *J* = 2.1 Hz, 1H), 4.03 (bs, 2H), 3.68 - 3.61 (dd, J1= 7.2 Hz, *J2* = 12.3 Hz 1H), 3.40 (s 3H), 3.37 - 3.28 (m, 3H), 3.02 (dd, J1= 8.4 Hz, *J2* = 18.6 Hz 1H), 2.75 (dd, J1= 2.7 Hz, J2= 15.9 Hz 1H), 2.58 - 2.50 (m, 3H), 2.32 (s, 3H), 2.01 (s, 6H), 1.94 - 1.67 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 165.0, 146.8, 144.6, 142.9, 141.0, 140.9, 139.8, 132.0, 130.3, 129.4, 128.5, 128.3, 126.0, 120.8, 120.1, 117.4, 116.1, 113.0, 111.5, 101.7, 60.5, 58.7, 56.3, 56.2, 55.2, 55.0, 41.5, 40.4, 39.5, 37.7, 31.0, 29.6, 26.4, 25.3, 15.5, 9.2.

ESI-MS m/z: Calcd. for $C_{37}H_{39}ClN_4O_7$: 686.2. Found $(M+1)^+$: 687.2.

Example 131



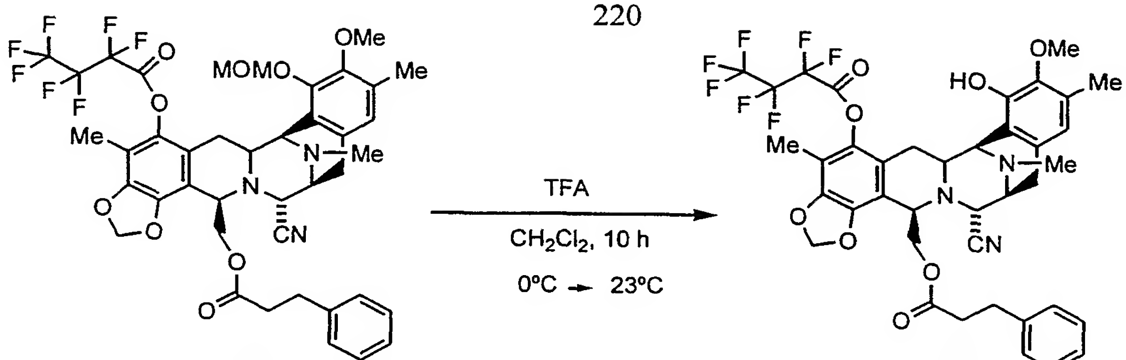
To a solution of **133** (94 mg, 0.126 mmol) in CH_2Cl_2 (1 mL), trifluoroacetic acid (385 µL, 5.0 mmol) was added at 0 °C and the reaction mixture was stirred for 2.5 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to give **137** (118 mg, 97 %) as a white solid which was used in following steps with no further purification. Rf: 0.24 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.14 (m, 3H), 7.05-7.03 (m, 2H), 6.44 (s, 1H), 5.98 (d, J = 1.5 Hz, 1H), 5.92 (d, J = 1.5 Hz, 1H), 5.82 (s, 1H), 5.20 (t, J = 4.8 Hz, 1H), 4.07 (d, J = 2.1 Hz, 1H), 5.82 (s, 1H), 5.20 (t, J = 4.8 Hz, 1H), 4.07 (d, J = 2.1 Hz, 1H), 4.01 (bs, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.93-3.84 (m, 2H), 3.63 (ddd, $J1$ = 1.5 Hz, $J2$ = 6.9 Hz, $J3$ = 12 Hz, 1H), 3.44 (bs, 3H), 3.37-3.26 (m, 3H), 3.11-3.06 (m, 2H), 3.01 (dd, $J1$ = 8.4 Hz, $J2$ = 18.3 Hz, 1H), 2.80 (brd, J = 13.8 Hz, 1H), 2.58-2.47 (m, 3H), 2.29 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.93-1.68 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 168.0, 146.7, 144.6, 142.8, 142.1, 141.0, 140.8, 140.1, 130.7, 129.0, 128.2, 126.0, 122.2, 120.9, 116.7, 114.7, 113.1, 111.7, 102.3, 101.7, 72.0, 60.4, 59.1, 56.4, 56.3, 55.7, 55.2, 41.7, 40.3, 38.8, 37.8, 37.1, 31.0, 26.4, 25.2, 15.5, 9.4.

ESI-MS m/z: Calcd. for $C_{38}H_{41}ClN_4O_7$: 700.2. Found $(M+23)^+$: 723.1.

Example 132

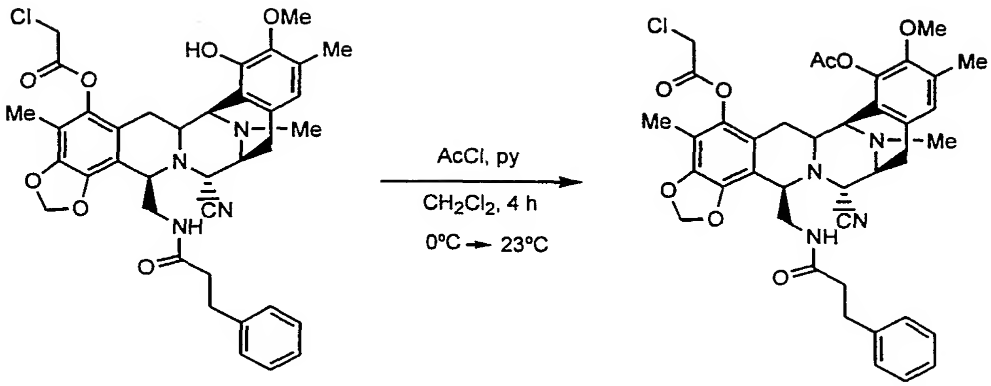


134 **138**

To a solution of **134** (46 mg, 0.054 mmol) in CH_2Cl_2 (1 mL), trifluoroacetic acid (166 µL, 2.16 mmol) was added at 0 °C and the reaction mixture was stirred for 10 h at 23°C. The reaction was quenched at 0°C with saturated aqueous sodium bicarbonate (15 mL) and extracted with ethyl acetate (2 x 10 mL). The combined organic layers were dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure to give **138** (35 mg, 80 %) as a white solid which was used in following steps with no further purification. Rf: 0.26 (Hex:EtOAc 1:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 - 7.12 (m, 3H), 7.04 - 7.01 (m, 2H), 6.45 (s, 1H), 6.03 (d, J = 1.5 Hz, 1H), 5.97 (d, J = 1.5 Hz, 1H), 5.64 (s, 1H), 4.98 (m, 1H), 4.09 (d, J = 2.1 Hz, 1H), 4.03 (bs, 1H), 3.98 (d, J = 2.4 Hz, 1H), 3.75 (dd, J1= 9.6 Hz, $J2$ = 14.1 Hz, 1H), 3.35 (s, 3H), 3.29 - 3.24 (m, 3H), 3.04 (dd, J1= 7.8 Hz, $J2$ = 18.0 Hz, 1H), 2.74 (dd, J1= 3.0 Hz, $J2$ = 16.8 Hz, 1H), 2.57 - 2.45 (m, 3H), 2.30 (s, 3H), 2.03 (s, 6H), 1.92 - 1.64 (m, 3H). ESI-MS m/z: Calcd. for $C_{39}H_{37}F_7N_4O_7$: 806.7. Found $(M+1)^+$: 807.3.

Example 133



136

139

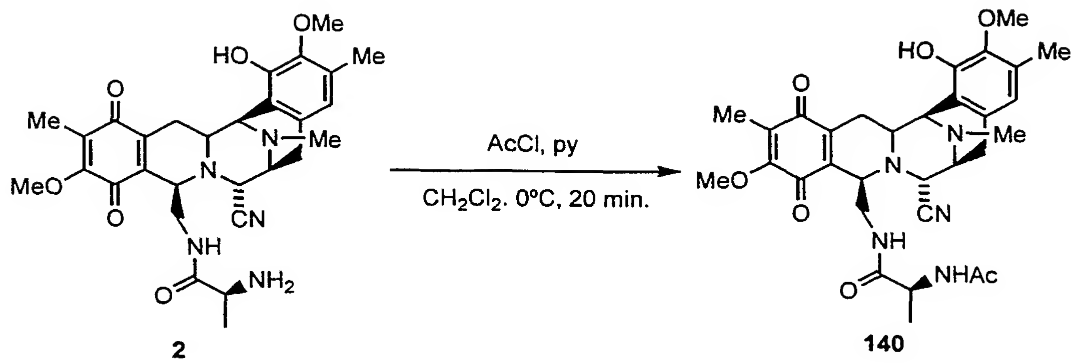
To a solution of **136** (45 mg, 0.065 mmol) in CH_2Cl_2 (0.3 mL), acetyl chloride (4.65 μL, 0.065 mmol), and pyridine (5.2 μL, 0.065 mmol) were added at 0 °C. The reaction mixture was stirred for 4 h and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (7 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient Hex:EtOAc 5:1 to EtOAc) to afford **139** (27 mg, 57 %) as a white solid.

Rf: 0.36 (Hex:EtOAc 1:2).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 - 7.14 (m, 3H), 7.07 - 7.04 (m, 2H), 6.84 (s, 1H), 6.00 (d, J = 1.2 Hz, 1H), 5.94 (d, J = 1.2 Hz, 1H), 4.94 (t, J = 5.1 Hz, 1H), 4.39 - 4.38 (m, 2H), 4.02 (bs, 2H), 3.67 (d, J = 3 Hz, 1H), 3.60-3.54 (m, 1H), 3.47-3.35 (m, 3H), 3.42 (s, 3H), 3.26 (dt, J_1 = 4.8 Hz, J_2 = 8.7 Hz 1H), 3.02 (dd, J_1 = 8.1 Hz, J_2 = 18.3 Hz, 1H), 2.64 - 2.38 (m, 3H), 2.35 (s, 3H), 2.25 (s, 3H), 2.06 (s, 3H), 2.03 (s, 3H), 1.95 - 1.69 (m, 3H).

ESI-MS m/z: Calcd. for $C_{39}H_{41}ClN_4O_8$: 729.2. Found $(M+23)^+$: 752.3.

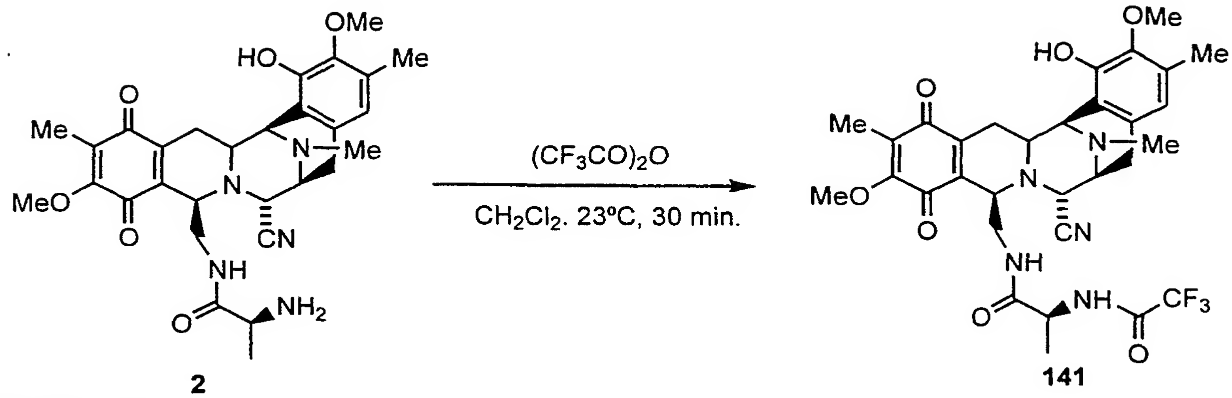
Example 134



To a solution of **2** (15 mg, 0.0273 mmol) in CH_2Cl_2 (0.2 mL), acetyl chloride (1.94 μL, 0.0273 mmol), and pyridine (2.20 μL, 0.0273 mmol) were added at 0 °C. The reaction mixture was stirred for 20 minutes and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAcMeOH 5:1) to afford **140** (9 mg, 56 %) as a light yellow solid. Rf: 0.56 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.52 (s, 1H), 6.40 (s, 1H), 5.73 (d, J= 7.5 Hz, 1H), 4.95 (d, J= 6.9 Hz, 1H), 4.20 (d, J= 1.5 Hz, 1H), 4.00 (s, 3H), 3.86 (d, J= 4.5 Hz, 1H), 3.79 (s, 3H), 3.78-3.77 (m, 1H), 3.40-3.35 (m, 2H), 3.24 (dt, , J_1= 3.6 Hz, J_2= 11.4 Hz, 1H), 3.17 (d, J= 7.8 Hz, 1H), 3.11 (d, J= 7.5 Hz, 1H), 3.04 (dd, J_1= 3.6 Hz, J_2= 18.6 Hz, 1H), 2.92 (dt, , J_1= 3.3 Hz, J_2= 14.1 Hz, 1H), 2.43 (d, J= 18.0 Hz, 1H), 2.37 (s, 3H), 2.29 (s, 3H), 1.89 (s, 3H), 1.79 (s, 3H), 1.75 (dd, J_1= 2.7 Hz, J_2= 6.9 Hz, 1H), 0.99 (d, J= 7.5 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{31}H_{37}N_5O_7$: 591.6. Found $(M+1)^+$: 592.3.



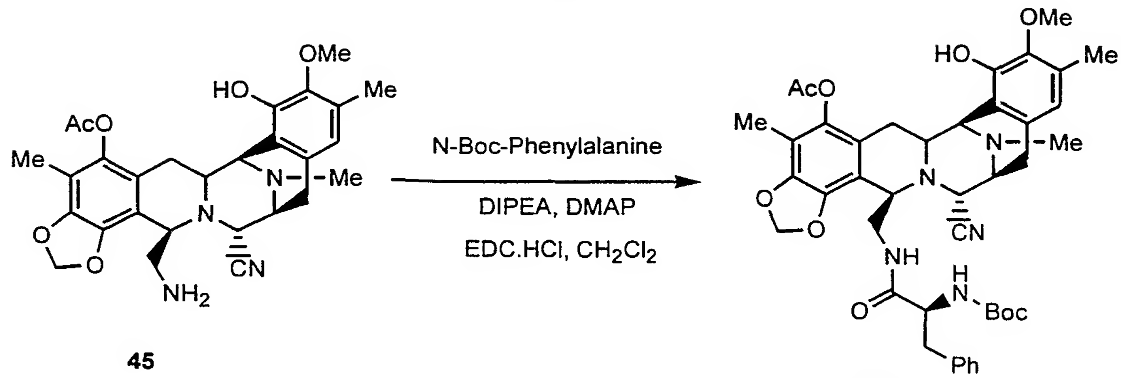
Example 135

To a solution of **2** (15 mg, 0.0273 mmol) in CH_2Cl_2 (0.2 mL), trifluoroacetyl anhydride (3.85 μL, 0.0273 mmol was added at 23 °C. The reaction mixture was stirred for 30 minutes and then, the solution was diluted with CH_2Cl_2 (15 mL) and washed with 0.1 N HCl (5 mL). The organic layer was dried over sodium sulphate, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, gradient EtOAc to EtOAcMeOH 4:1) to afford **141** (12.1 mg, 69 %) as a light yellow solid. Rf: 0.73 (EtOAc:MeOH 5:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J= 6.6 Hz, 1H), 6.56 (s, 1H), 5.11 (d, J= 6.6 Hz, 1H), 4.47 (bs, 1H), 4.23 (bs, 1H), 3.97 (s, 3H), 3.93 (bs, 1H), 3.85-3.81 (m, 1H), 3.77 (s, 3H), 3.40-3-36 (m, 2H), 3.23 (dd, J_1= 7.2 Hz, J_2= 18.6 Hz, 1H), 3.13-3.08 (m, 3H), 1.86 (s, 3H), 1.74 (dd, J_1= 10.8 Hz, J_2= 16.8 Hz, 1H), 1.07 (d, J= 6.9 Hz, 3H).

ESI-MS m/z: Calcd. for $C_{31}H_{34}F_3N_5O_7$: 645.6. Found $(M+1)^+$: 646.3.

Example 136



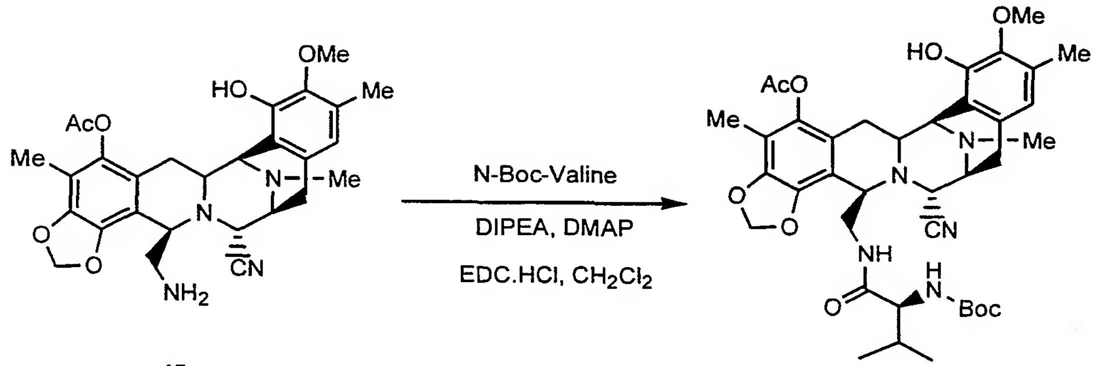
45

174

To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), N-Boc-Phenylalanine (22.9 mg, 0.086mmol) and DMAP (0.7 mg, 0.006 mmol) were added at room temperature and the reaction mixture was stirred for 4h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **174** (17 mg, 38%) as a white solid.

Rf = 0.35 Hex:AcOEt 1:2.
^{1}H NMR (300 MHz, $CDCl_3$) 7.24-7.15 (m, 3H), 7.05-7.02 (m, 2H), 6.43 (s, 1H), 5.88 (s, 1H), 5.78 (s, 1H), 5.64 (s, 1H), 5.63 (bs, 1H), 4.80 (bs, 1H), 3.98 (s, 1H), 3.85 (bs, 2H), 3.75 (bs, 1H), 3.58 (bs, 1H), 3.53 (bs, 3H), 3.38 (m, 1H), 3.17-3.10 (m, 3H) 2.90 (dd, J_1 = 8.7 Hz, J_2 = 17.7 Hz, 1H), 2.73 (d, J = 14.4 Hz, 1H), 2.57 (m, 1H), 2.43-2.37 (m, 1H), 2.25 (s, 3H), 2.24 (s, 3H), 2.10 (s, 3H), 1.94 (s, 3H), 1.76 (dd, J_1 = 12.3 Hz, J_2 = 15.6 Hz, 1H), 1.19 (bs, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) 171.2, 168.8, 146.6, 144.6, 142.8, 140.6, 137.0, 130.7, 129.5, 129.0, 128.4, 126.8, 121.1, 121.0, 117.8, 116.7, 113.3, 111.8, 101.5, 60.5, 59.7, 57.0, 56.4, 55.3, 41.9, 41.6, 38.7, 31.6, 29.7, 28.2, 26.5, 25.2, 22.6, 20.3, 15.7, 14.1, 9.3.
ESI-MS m/z: Calcd. for $C_{42}H_{49}N_5O_9$: 767.87. Found $(M+1)^+$: 768.3.

Example 137



45

175

To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), N-Boc-Valine (18.8 mg, 0.086 mmol) and DMAP (0.7 mg, 0.006 mmol) were added at room temperature and the reaction mixture was stirred for 4 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **175** (18 mg, 43%) as a white solid.

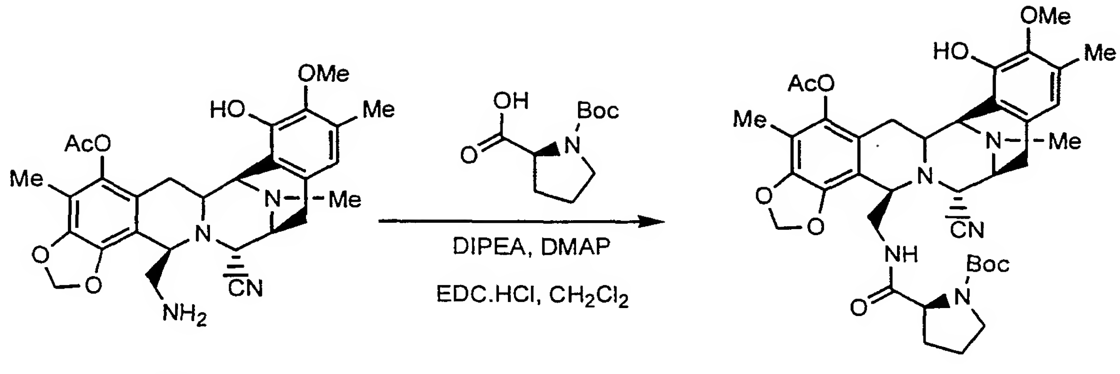
Rf = 0.25 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (s, 1H), 5.97 (s, 1H), 5.82 (s, 1H), 5.73 (bs, 1H), 5.50 (bs, 1H), 4.82 (bs, 1H), 4.15 (bs, 1H), 4.03 (bs, 1H), 3.96 (bs, 1H), 3.72 (s, 3H), 3.61 (m, 1H), 3.41-3.15 (m, 3H), 2.96 (dd, J_1 = 8.4 Hz, J_2 = 18.3 Hz, 1H), 2.72 (d, J = 16.5 Hz, 1H), 2.53 (d, J = 18 Hz, 1H), 2.25 (s, 3H), 2.21 (s, 3H), 1.93 (s, 3H), 1.81 (dd, J_1 = 14.1 Hz, J_2 = 14.7 Hz, 1H), 1.34 (s, 9H), 0.83-0.76 (m, 2H), 0.61 (d, J = 6.3 Hz, 3H), 0.54 (d, J = 6.3 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 168.7, 155.4, 146.8, 144.5, 142.9, 140.7, 130.7, 128.8, 121.0, 120.6, 117.7, 116.8, 113.3, 111.9, 101.4, 60.6, 60.0, 59.3, 57.2, 56.3, 55.2, 41.7, 29.7, 29.3, 28.2, 26.2, 25.2, 22.6, 20.3, 18.9, 17.7, 15.7, 14.1, 9.3.

ESI-MS m/z: Calcd. for $C_{38}H_{49}N_5O_9$: 719.82. Found $(M+1)^+$: 720.3.

Example 138



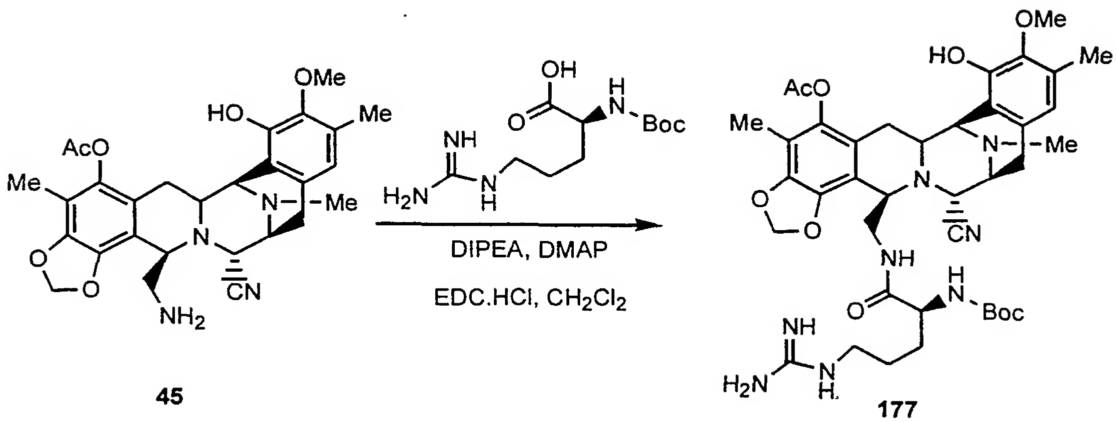
To a solution of **45** (38 mg, 0.073 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (19.0 mL, 0.109 mmol), EDC·HCl (34.9 mg, 0.182 mmol), N-Boc-Proline (23.5 mg, 0.109 mmol) and DMAP (0.8 mg, 0.007 mmol) were added at 23 °C and the reaction mixture was stirred for 4.5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:1) to afford **176** (33 mg, 63%) as a white solid.

Rf = 0.14 Hex:EtOAc 1:2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (s, 1H), 6.02 (bs, 1H), 5.90 (s, 1H), 5.74 (s, 1H), 4.19 (bs, 1H), 4.09 (bs, 1H), 3.98 (bs, 1H), 3.76 (s, 3H), 3.38 (d, J = 6 Hz, 2H), 3.22 (d, J = 11.7 Hz, 1H), 3.15-2.99 (m, 2H), 2.80 (d, J = 15.3 Hz, 1H), 2.63-2.58 (m, 1H), 2.32 (s, 3H), 2.26 (s, 6H), 1.99 (s, 3H), 1.78-1.62 (m, 1H), 1.50-0.83 (m, 7H), 1.21 (s, 9H).

ESI-MS m/z: Calcd. for $C_{38}H_{47}N_5O_9$: 717.81. Found $(M+1)^+$: 718.3.

Example 139



45

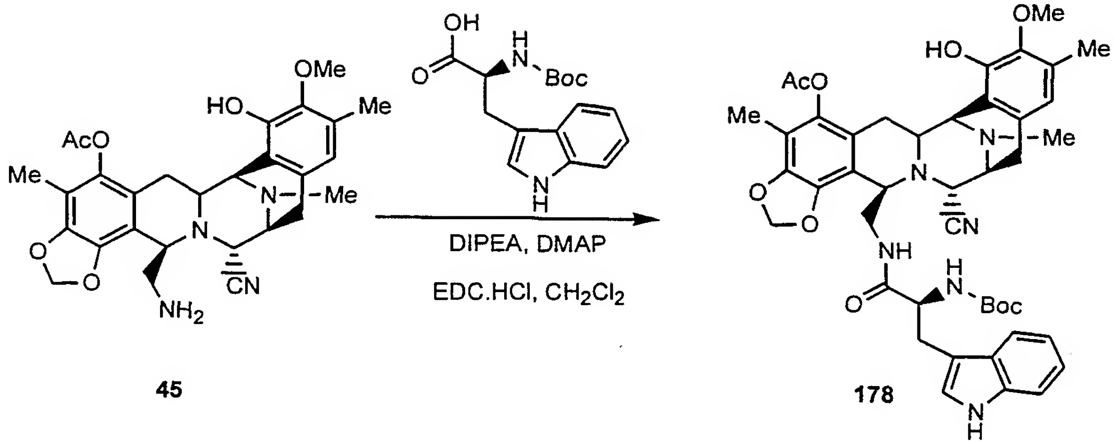
To a solution of **45** (50 mg, 0.144 mmol) in CH_2Cl_2 (0.96 mL), DIPEA (41.8 mL, 0.240 mmol), EDC·HCl (46.0 mg, 0.240 mmol), N-Boc-Arginine hidrochloride hydrate (47.2 mg, 0.144 mmol) and DMAP (1.1 mg, 0.01 mmol) were added at 23 °C and the reaction mixture was stirred for 4 h. Then, the solvent was removed under vacuum and the residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **177** (58 mg, 78%) as a white solid.

Rf = 0.40 MeOH:EtOAc 1:5.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (bs, 1H), 6.95 (bs, 3H), 6.54 (bs, 1H), 6.48 (s, 1H), 6.07 (s, 1H), 6.00 (bs, 1H), 5.88 (s, 1H), 5.11 (bs, 1H), 4.23 (s, 1H), 4.08 (s, 1H), 4.02 (s, 1H), 3.76 (s, 3H), 3.70 (bs, 1H), 3.48 (bs, 1H), 3.37 (d, J = 6.9 Hz, 1H), 3.18 (d, J = 10.2 Hz, 1H), 3.00-2.94 (m, 3H), 2.82-2.70 (m, 2H), 2.34 (s, 3H), 2.25 (s, 6H), 1.99 (s, 3H), 1.73 (brt, J = 14.1 Hz, 1H), 1.40 (s, 9H), 1.25 (bs, 3H), 0.95-0.85 (m, 2H).

ESI-MS m/z: Calcd. for $C_{39}H_{52}N_8O_9$: 776.88. Found $(M+1)^+$: 777.3.

Example 140



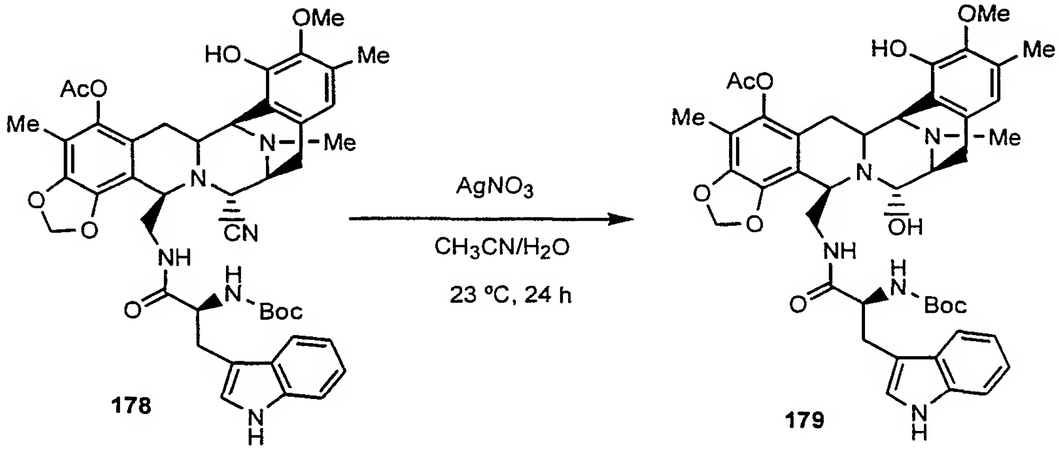
To a solution of **45** (50 mg, 0.096 mmol) in CH_2Cl_2 (1.44 mL), DIPEA (25.8 mL, 0.144 mmol), EDC·HCl (46.0 mg, 0.240 mmol), N-Boc-Tryptophan (43.8 mg, 0.144 mmol) and DMAP (1.2 mg, 0.009 mmol) were added at 23 °C and the reaction mixture was stirred for 4 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **178** (57 mg, 74%) as a white solid.

Rf = 0.12 Hex:EtOAc 1:1.

^1H NMR (300 MHz, $CDCl_3$) δ 8.50 (bs, 1H), 7.73-7.71 (m, 1H), 7.13-7.12 (m, 3H), 6.51 (s, 1H), 5.72 (s, 1H), 5.36 (bs, 1H), 5.28 (bs, 1H), 4.95 (bs, 1H), 4.41 (bs, 1H), 4.05 (s, 1H), 3.70 (s, 3H), 3.50 (bs, 2H), 3.30-3.17 (m, 4H), 2.89-2.82 (m, 3H), 2.40 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H), 2.03 (s, 3H), 1.49 (s, 9H), 1.26-1.25 (m, 2H).

ESI-MS m/z: Calcd. for $C_{44}H_{50}N_6O_9$: 806.90. Found $(M+1)^+$: 807.3.

Example 141



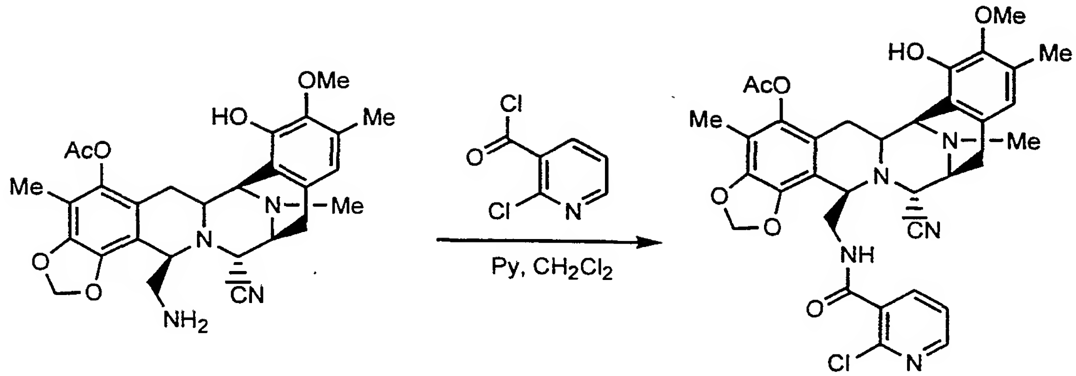
To a solution of **178** (43 mg, 0.053 mmol) in CH_3CN/H_2O (3 mL/2 mL), $AgNO_3$ (271 mg, 1.60 mmol) was added and the reaction was stirred at 23°C for 17 h. Then, Aq sat NaCl (10 mL) and Aq sat $NaHCO_3$ (10 mL) were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **179** (24 mg, 56%) as a white solid.

Rf = 0.38 EtOAc:MeOH 5:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.66 (bs, 1H), 7.25-7.21 (m, 1H), 7.16-7.09 (m, 2H), 6.45 (s, 1H), 5.75 (bs, 1H), 5.55 (bs, 1H), 5.45 (s, 1H), 5.25 (bs, 1H), 4.36 (bs, 1H), 4.16 (bs, 1H), 4.05 (bs, 1H), 3.95 (s, 1H), 3.69 (s, 3H), 3.35-3.02 (m, 6H), 2.83-2.73 (m, 3H), 2.35 (s, 3H), 2.24 (s, 3H), 2.19 (s, 3H), 1.99 (s, 3H), 1.77 (dd, J_1 = 12 Hz, J_2 = 15.3 Hz 1H).

ESI-MS m/z: Calcd. for $C_{43}H_{51}N_5O_{10}$: 797.89. Found $(M-17)^+$: 780.

Example 142



45

180

To a solution of **45** (50 mg, 0.0960 mmol) in CH_2Cl_2 (0.7 mL), 2-Chloronicotinoyl chloride (17.7 mg, 0.101 mmol) and pyridine (8.1mL, 0.101 mmol) were added at 0 °C. The reaction mixture was stirred for 1.5 h and then, the solution was diluted with CH_2Cl_2 (5 mL) and washed with 0.1 N HCl (3 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:1) to afford **180** (45 mg, 71%) as a white solid.

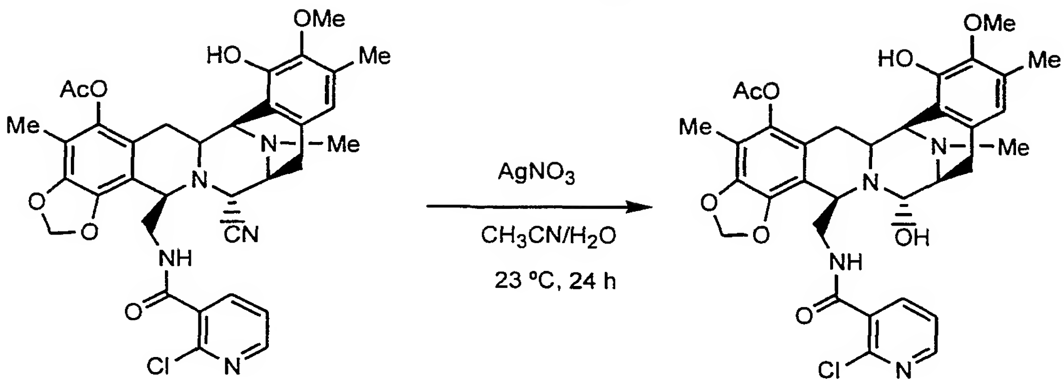
Rf = 0.18 Hex:EtOAc 1:2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.32-8.29 (m, 1H), 7.38-7.34 (m, 1H), 7.14-7.09 (m, 1H), 6.14 (s, 1H), 5.97 (d, J = 1.2 Hz, 1H), 5.92-5.91 (m, 2H), 5.75 (d, J = 2.1 Hz, 1H), 4.18 (d, J = 2.1 Hz, 1H), 4.15 (s, 1H), 4.07 (s, 1H), 3.91-3.73 (m, 2H), 3.68 (s, 3H), 3.36 (d, J = 7.5 Hz, 1H), 3.31 (dt, J_1 = 2.4 Hz, J_2 = 11.7 Hz, 1H), 2.92 (dd, J_1 = 8.1 Hz, J_2 = 18 Hz, 1H), 2.80 (d, J = 16.2 Hz, 1H), 2.58 (d, J = 18 Hz, 1H), 2.31 (s, 3H), 2.27 (s, 3H), 1.99 (s, 3H), 1.91 (s, 3H) 1.97-1.83 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.6, 164.8, 150.3, 147.2, 146.5, 144.6, 142.5, 140.6, 139.0, 130.9, 130.5, 128.8, 122.3, 120.8, 120.3, 117.6, 116.3, 112.7, 112.1, 101.6, 60.6, 58.8, 56.5, 56.3, 55.6, 55.1, 41.6, 39.8, 31.5, 26.2, 24.9, 20.3, 15.5, 9.3.

ESI-MS m/z: Calcd. for $C_{34}H_{34}ClN_5O_7$: 659.2. Found $(M+1)^+$: 660.1.

Example 143



180 181

To a solution of **180** (39 mg, 0.059 mmol) in CH_3CN/H_2O (3 mL/2 mL), $AgNO_3$ (301mg, 1.77 mmol) was added and the reaction was stirred at 23°C for 17 h. Then, Aq sat NaCl (10 mL) and Aq sat NaHCO3 (10 mL) solutions were added at 0°C and the mixture was stirred for 15 min, filtered through a pad of celite and washed with CH_2Cl_2 (20 mL). The solution was decanted and the organic layer was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, EtOAc:MeOH 5:1) to afford **181** (28 mg, 73%) as a white solid.

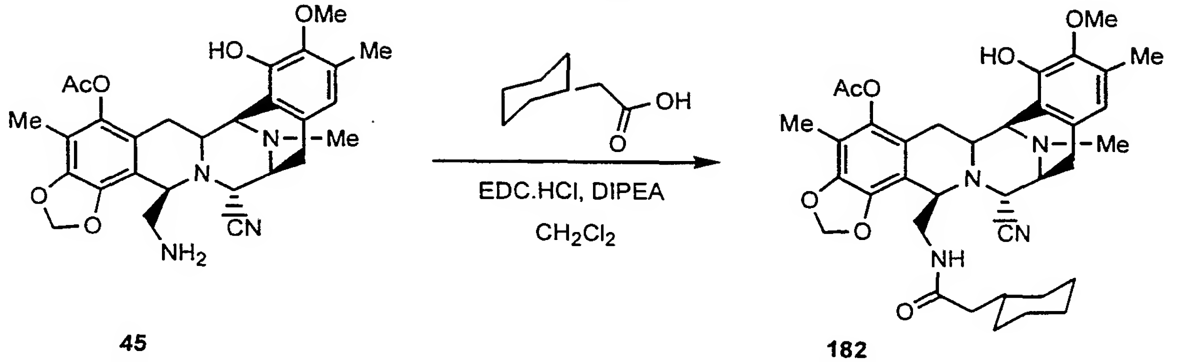
Rf = 0.24, EtOAc:MeOH 5:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33-8.31 (m, 1H), 7.40-7.35 (m, 1H), 7.16-7.09 (m, 2H), 6.20 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.96 (s, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.63 (bs, 1H), 4.60 (bs, 1H), 4.47 (bs, 1H), 4.02-3.95 (m, 2H), 3.69 (s, 3H), 3.65-3.56 (m, 1H), 3.48 (s, 3H), 3.43-3.38 (m, 1H), 3.17 (brd, J = 7.2 Hz, 1H), 2.88 (dd, J_1 = 8.7 Hz, J_2 = 18.3 Hz, 1H), 2.74 (d, J = 15.3 Hz, 1H), 2.40 (d, J = 18.3 Hz, 1H), 2.32 (s, 3H), 2.26 (s, 3H), 2.00 (s, 3H), 1.99 (s, 3H), 1.77 (dd, J_1 = 12 Hz, J_2 = 15 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 165.0, 150.0, 147.2, 146.5, 144.4, 142.5, 140.9, 138.7, 131.5, 130.2, 128.9, 122.3, 121.1, 120.7, 116.1, 114.4, 111.4, 101.5, 82.6, 60.6, 57.8, 56.2, 52.1, 41.6, 31.5, 26.4, 24.5, 22.6, 20.3, 15.6, 14.1, 9.3.

ESI-MS m/z: Calcd. for $C_{33}H_{35}ClN_4O_8$: 650.2 Found $(M-17)^+$: 633.3.

Example 144



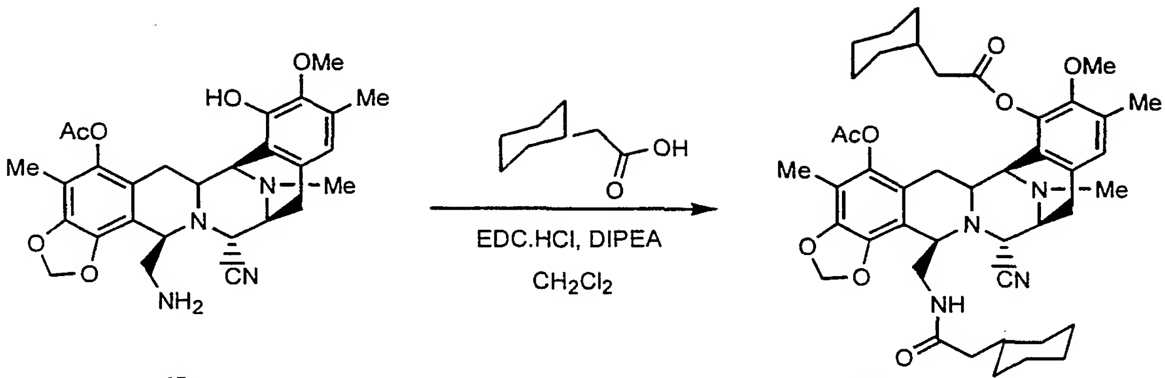
To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), cyclohexylacetic acid (12.2 mg, 0.086 mmol) and DMAP (0.7 mg, 0.006 mmol) were added at 0°C and the reaction mixture was stirred for 5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **182** (10 mg, 27%) as a white solid.

Rf = 0.11 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.91 (d, J = 1.2 Hz, 1H), 5.75 (s, 1H), 5.02-4.91 (m, 1H), 4.11 (bs, 1H), 4.04 (d, J = 2.1 Hz, 1H), 4.01 (bs, 1H), 3.78 (s, 3H), 3.72-3.69 (m, 1H), 3.38-3.29 (m, 3H), 3.05 (dd, J_1 = 7.8 Hz, J_2 = 18.0 Hz, 1H), 2.77 (d, J = 15.6 Hz, 1H), 2.54 (d, J = 18.6 Hz, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H), 1.79 (dd, J_1 = 11.7 Hz, J_2 = 15.6 Hz, 1H), 1.59-0.61 (m, 13H).

ESI-MS m/z: Calcd. for $C_{36}H_{44}N_4O_7$: 644.76. Found $(M+1)^+$: 645.3.

Example 145



45

183

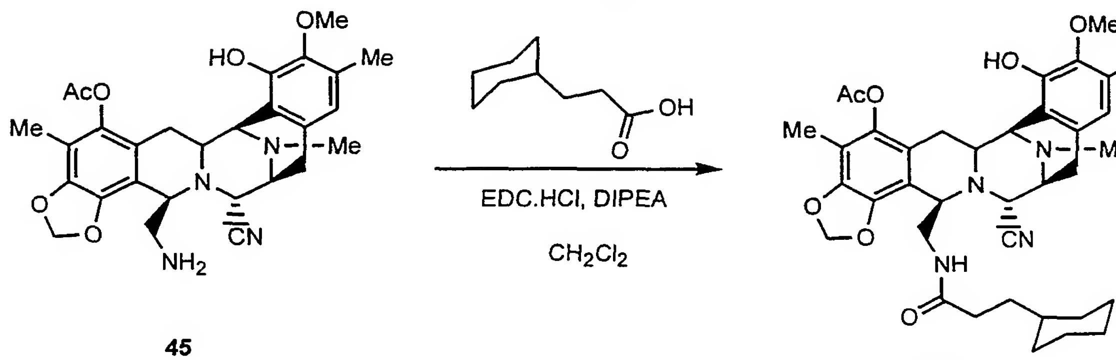
To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), cyclohexylacetic acid (12.2 mg, 0.086 mmol) and DMAP (0.7 mg, 0.006 mmol) were added at 0°C and the reaction mixture was stirred for 5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **183** (17 mg, 38%) as a white solid.

Rf = 0.13 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 4.95 (t, J = 5.7 Hz, 1H), 4.08 (bs, 1H), 4.00 (bs, 1H), 3.71 (s, 3H), 3.64 (d, J = 1.8 Hz, 2H), 3.38 (d, J = 6.6 Hz, 1H), 3.33-3.32 (m, 1H), 3.27 (d, J = 11.7 Hz, 1H), 3.06 (dd, J_1 = 7.8 Hz, J_2 = 18.0 Hz, 1H), 2.65-2.59 (m, 1H), 2.50-2.47 (m, 1H), 2.35 (s, 3H), 2.27 (s, 6H), 1.99 (s, 3H), 1.78-1.74 (m, 1H) 1.60-0.62 (m, 26H).

ESI-MS m/z: Calcd. for $C_{44}H_{56}N_4O_8$: 768.94. Found $(M+1)^+$: 769.3.

Example 146



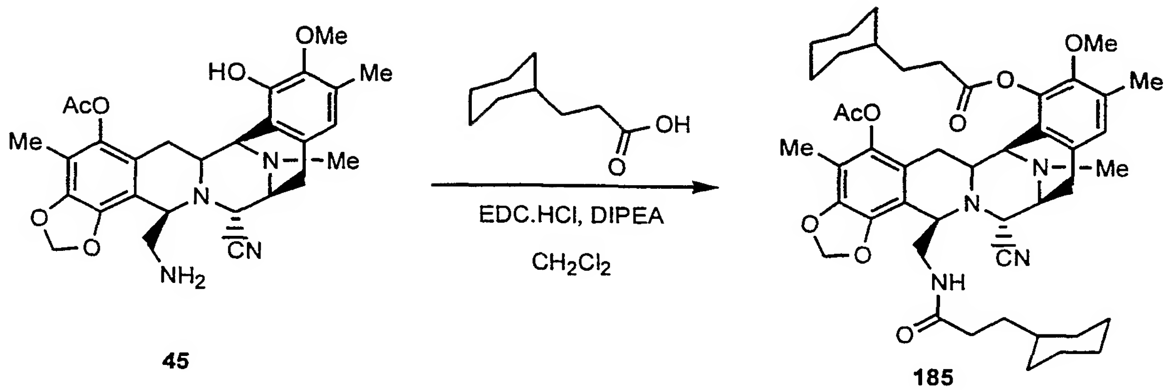
45 **184**

To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), cyclohexylpropionic acid (13.5 mg, 0.086 mmol) and DMAP (0.7 mg, 0.006 mmol) were added at 0°C and the reaction mixture was stirred at 23 °C for 6 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **184** (15 mg, 39%) as a white solid.

Rf = 0.15 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.50 (s, 1H), 5.98 (s, 1H), 5.91 (s, 1H), 5.74 (s, 1H), 5.01 (t, J = 5.1 Hz, 1H), 4.09 (bs, 1H), 4.06 (s, 1H), 4.02 (bs, 1H), 3.76 (s, 3H), 3.64-3.58 (m, 1H), 3.42-3.41 (m, 1H), 3.36 (d, J = 7.5 Hz, 1H), 3.28 (d, J = 12.3 Hz, 1H), 3.05 (dd, J_1 = 8.6 Hz, J_2 = 18 Hz, 1H), 2.79 (d, J = 14.7 Hz, 1H), 2.57 (d, J = 18 Hz, 1H), 2.32 (s, 3H), 2.30 (s, 3H), 2.25 (s, 3H), 1.99 (s, 3H), 1.77 (dd, J_1 = 12.0 Hz, J_2 = 15.9 Hz, 1H), 1.62-0.71 (m, 15H). ESI-MS m/z: Calcd. for $C_{37}H_{46}N_4O_7$: 658.78. Found $(M+1)^+$: 659.3.

Example 147



To a solution of **45** (30 mg, 0.058 mmol) in CH_2Cl_2 (0.87 mL), DIPEA (15.0 mL, 0.086 mmol), EDC·HCl (27.6 mg, 0.145 mmol), cyclohexylpropionic acid (13.5 mg, 0.086 mmol) and DMAP (0.7 mg, 0.006 mmol) were added at 0°C and the reaction mixture was stirred for 6 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **185** (21 mg, 46%) as a white solid.

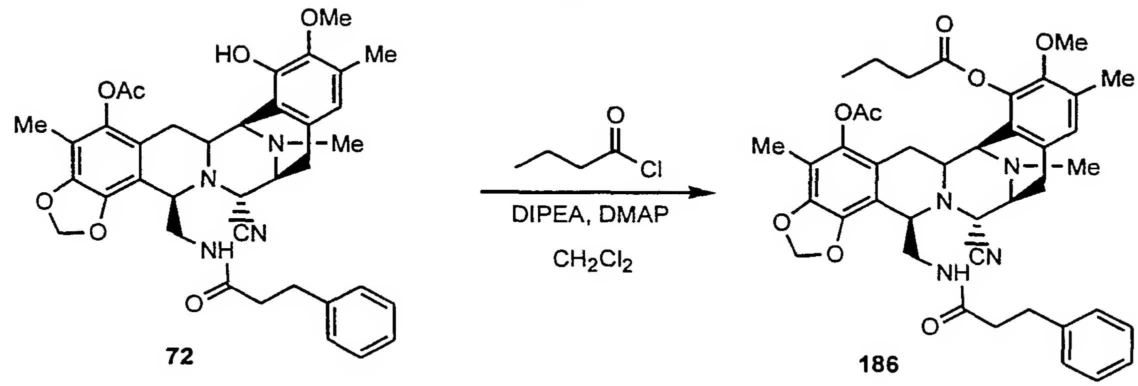
Rf = 0.17 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (s, 1H), 5.99 (s, 1H), 5.92 (s, 1H), 4.97 (t, J = 5.4 Hz, 1H), 4.10 (d, J = 2.4 Hz, 1H), 4.01 (bs, 1H), 3.70 (s, 3H), 3.64 (d, J = 2.4 Hz, 1H), 3.51 (bs, 1H), 3.37 (d, J = 8.1 Hz, 1H), 3.23 (d, J = 11.1 Hz, 1H), 3.02 (dd, J_1 = 7.8 Hz, J_2 = 18 Hz, 1H), 2.69-2.59 (m, 4H), 2.35 (s, 3H), 2.26 (s, 6H), 2.00 (s, 3H), 1.76-0.72 (m, 30H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 171.5, 168.2, 147.9, 144.7, 142.5, 140.7, 140.3, 130.9, 130.6, 127.7, 123.3, 120.0, 117.5, 113.1, 111.9, 101.6, 60.5, 59.0, 57.3, 56.7, 55.2, 55.0, 41.6, 39.9, 37.2, 33.5, 33.0, 32.9, 32.9, 32.8, 32.5, 32.4, 31.9, 31.7, 29.7, 29.3, 26.6, 26.5, 26.2, 24.9, 20.3, 15.8, 14.1, 9.4.

ESI-MS m/z: Calcd. for $C_{46}H_{60}N_4O_8$: 796.4. Found $(M+1)^+$: 797.5.

Example 148



To a solution of **72** (111 mg, 0.162 mmol) in CH_2Cl_2 (0.81 mL), DIPEA (56.3 mL, 0.324 mmol), butyryl chloride (33.6 mL, 0.324 mmol) and DMAP (1.96 mg, 0.016 mmol) were added at 0 °C and the reaction mixture was stirred for 5 h at this temperature. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **186** (65.4 mg, 54%) as a white solid.

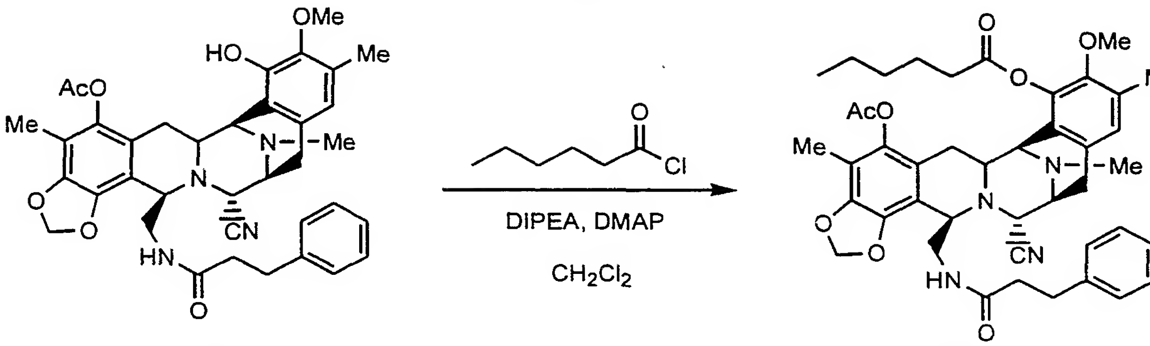
Rf = 0.21 Hex:EtOAc 1:2.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24-7.15 (m, 3H), 7.12-7.04 (m, 2H), 6.84 (s, 1H), 5.98 (d, J = 1.2 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 4.97 (t, J = 5.7 Hz, 1H), 4.03 (m, 3H), 3.63 (d, J = 2.7 Hz, 1H), 3.50 (m, 2H), 3.44 (s, 3H), 3.37 (d, J = 8.4 Hz, 1H), 3.24 (dt, J_1 = 2.7 Hz, J_2 = 11.7 Hz, 1H), 3.02 (dd, J_1 = 8.1 Hz, J_2 = 18.3 Hz, 1H), 2.65-2.54 (m, 7H), 2.35 (s, 3H), 2.25 (s, 3H), 2.07 (s, 3H), 2.02 (s, 3H), 1.87-1.75 (m, 3H), 1.08 (t, J = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 170.8, 168.2, 147.8, 144.7, 142.5, 140.8, 140.6, 140.3, 131.1, 130.5, 128.3, 128.2, 127.6, 126.0, 123.2, 117.5, 112.9, 111.8, 101.6, 60.2, 59.0, 57.3, 56.6, 55.1, 54.9, 41.5, 39.9, 37.8, 36.0, 31.0, 26.5, 24.8, 22.6, 20.2, 18.5, 15.6, 13.7, 9.3.

ESI-MS m/z: Calcd. for $C_{41}H_{46}N_4O_8$: 722.83. Found $(M+1)^+$: 723.2.

Example 149



72 187

To a solution of **72** (80 mg, 0.122 mmol) in CH_2Cl_2 (0.61 mL), DIPEA (64.0 mL, 0.367 mmol), hexanoyl chloride (49.5 mL, 0.367mmol) and DMAP (1.50 mg, 0.012 mmol) were added at 0 °C and the reaction mixture was stirred at this temperature for 5h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 6:4) to afford **187** (86.1 mg, 94%) as a white solid.

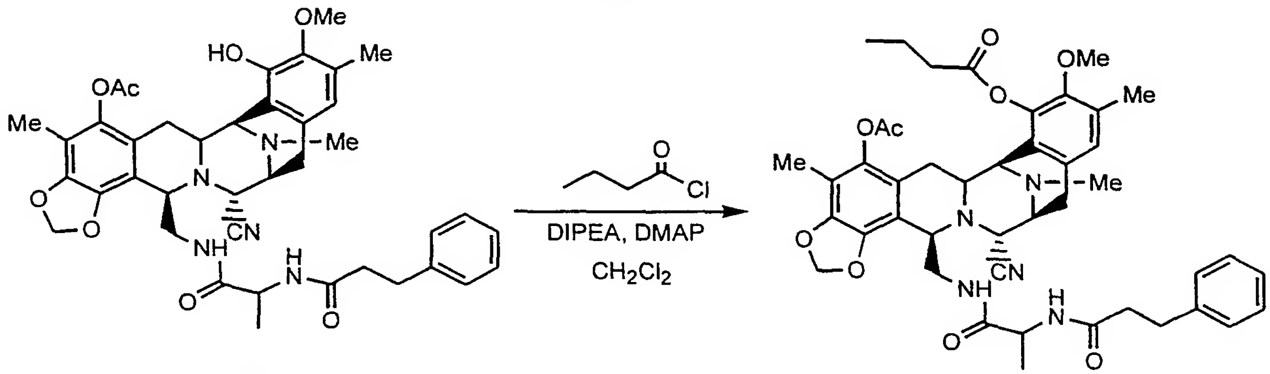
Rf = 0.25 Hex:EtOAc 1:2

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.06 (m, 3H), 6.99-6.97 (m, 2H), 6.77 (s, 1H), 5.91 (s, 1H), 5.85 (s, 1H), 4.90 (m, 1H), 3.96 (d, J = 3 Hz, 2H), 3.57-3.55 (m, 1H), 3.43 (bs, 2H), 3.36 (bs, 3H), 3.29 (brd, J = 10.5 Hz, 1H), 3.18 (d, J = 11.7 Hz, 1H), 2.97 (dd, J_1 = 4.8 Hz, J_2 = 12 Hz, 1H), 2.58-2.46 (m, 6H), 2.28 (s, 3H), 2.18 (s, 3H), 2.00 (s, 3H), 1.95 (s, 3H), 1.86-1.66 (m, 7H), 1.41-1.38 (m, 2H), 0.86-0.81 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 171.0, 168.2, 147.8, 144.7, 142.5, 140.8, 140.6, 140.3, 131.1, 130.5, 128.3, 128.2, 127.6, 126.0, 117.5, 112.9, 111.8, 101.6, 60.2, 59.0, 57.3, 56.6, 55.1, 55.0, 41.5, 39.9, 37.8, 34.1, 31.3, 31.1, 29.6, 24.8, 24.7, 22.3, 20.2, 15.6, 13.8.

ESI-MS m/z: Calcd. for $C_{43}H_{50}N_4O_8$: 750.88. Found $(M+1)^+$: 751.3.

Example 150



85 188

To a solution of **85** (80 mg, 0.110 mmol) in CH_2Cl_2 (0.55 mL), DIPEA (57.7 mL, 0.331 mmol), butyryl chloride (34.4 mL, 0.331mmol) and DMAP (1.30 mg, 0.011 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **188** (70.1 mg, 80%) as a white solid.

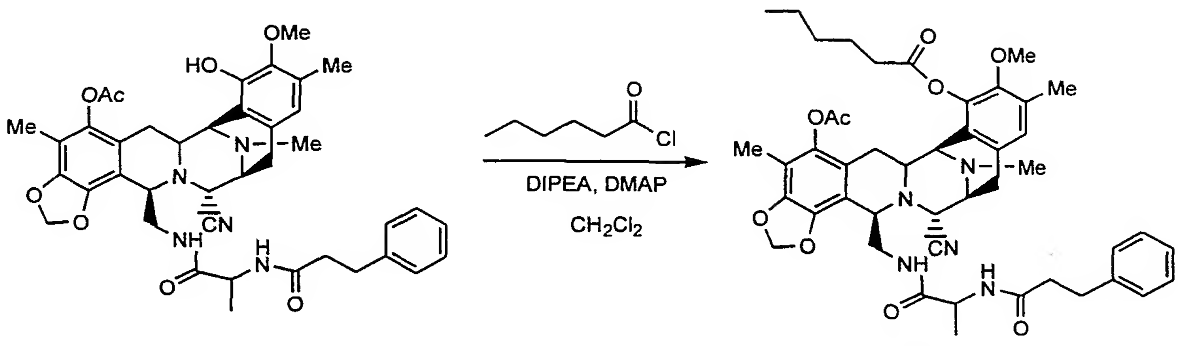
Rf = 0.54 MeOH:EtOAc 1:5.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.14 (m, 5H), 6.80 (s, 1H), 6.07 (d, J = 6.6 Hz, 1H), 6.00 (d, J = 1.5 Hz, 1H), 5.90 (d, J = 1.5 Hz, 1H), 5.35 (t, J = 5.4 Hz, 1H), 4.12 (d, J = 2.4 Hz, 1H), 4.05 (bs, 1H), 3.89 (brt, J = 6.9 Hz, 1H), 3.66 (s, 3H), 3.64-3.63 (m, 1H), 3.59-3.45 (m, 2H), 3.40 (brd, J = 7.8 Hz, 1H), 3.20 (dt, J_1 = 2.7 Hz, J_2 = 12 Hz, 1H), 3.00 (dd, J_1 = 8.1 Hz, J_2 = 18 Hz, 1H), 2.87 (t, J = 8.1 Hz, 2H), 2.71 (d, J = 18.6 Hz, 1H), 2.66-2.61 (m, 1H), 2.58 (t, J = 7.2 Hz, 2H), 2.41-2.35 (m, 2H), 2.33 (s, 3H), 2.23 (s, 3H), 2.21 (s, 3H), 2.00 (s, 3H), 1.90-1.77 (m, 3H), 1.08 (t, J = 7.2 Hz, 3H), 0.69 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.3, 170.8, 168.5, 147.7, 144.7, 142.5, 140.6, 140.5, 140.3, 131.0, 130.7, 128.4, 128.2, 127.7, 126.1, 123.1, 120.3, 117.5, 112.7, 111.8, 101.6, 60.3, 59.1, 57.3, 57.2, 55.4, 54.9, 48.2, 41.5, 39.5, 38.0, 36.0, 31.4, 26.8, 26.6, 24.6, 20.1, 18.5, 18.1, 15.7, 13.7, 9.2.

ESI-MS m/z: Calcd. for $C_{44}H_{51}N_5O_9$: 793.9. Found $(M+1)^+$: 794.3.

Example 151



85 189

To a solution of **85** (80 mg, 0.110 mmol) in CH_2Cl_2 (0.55 mL), DIPEA (57.7 mL, 0.331 mmol), hexanoyl chloride (46.3 mL, 0.331mmol) and DMAP (1.30 mg, 0.011 mmol) were added at 0 °C and the reaction mixture was stirred at 23°C for 5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed succesively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **189** (80 mg, 88%) as a white solid.

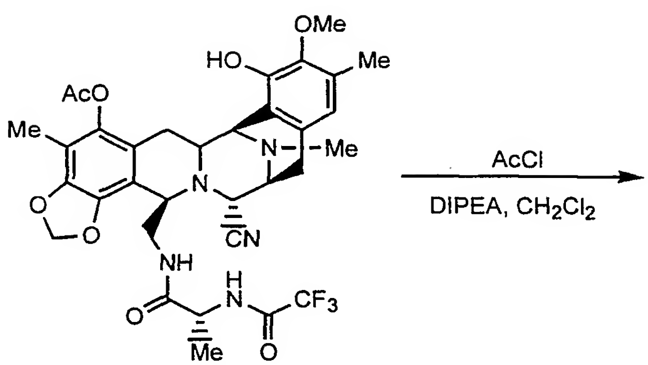
Rf = 0.23 Hex:EtOAc 1:3.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21-7.08 (m, 5H), 6.74 (s, 1H), 6.00 (d, J = 6.9 Hz, 1H), 5.94 (d, J = 1.5 Hz, 1H), 5.84 (d, J = 1.5 Hz, 1H), 5.24 (t, J = 5.4 Hz, 1H), 4.06 (bs, 1H), 4.00 (bs, 1H), 3.83 (t, J = 6 Hz, 1H), 3.59 (s, 3H), 3.57 (m, 1H), 3.53-3.40 (m, 2H), 3.33 (d, J = 7.8 Hz, 1H), 3.14 (d, J = 11.7 Hz, 1H), 2.94 (dd, J_1 = 8.4 Hz, J_2 = 18 Hz, 1H), 2.81 (t, J = 7.5 Hz, 2H), 2.65 (d, J = 18 Hz, 1H), 2.60-2.54 (m, 1H), 2.52 (t, J = 7.2 Hz, 2H), 2.35-2.29 (m, 2H), 2.27 (s, 3H), 2.17 (s, 3H), 2.15 (s, 3H), 1.95 (s, 3H), 1.76-1.60 (m, 3H), 1.35-1.29 (m, 2H), 1.84 (m, 2H), 0.85-0.78 (m, 3H), 0.62 (t, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 171.3, 171.1, 168.4, 147.8, 144.8, 142.6, 140.7, 140.5, 131.2, 130.6, 128.4, 128.3, 127.7, 126.2, 123.1, 120.3, 117.5, 112.6, 112.0, 101.7, 60.4, 59.1, 57.4, 57.2, 55.4, 54.9, 48.3, 41.5, 39.6, 38.1, 34.1, 33.6, 31.5, 31.3, 26.7, 24.7, 22.3, 20.2, 18.2, 15.7, 13.9, 9.3.

ESI-MS m/z: Calcd. for $C_{46}H_{55}N_5O_9$: 821.96. Found $(M+1)^+$: 822.3.

Example 152



53 190

To a solution of **53** (100 mg, 0.145 mmol) in CH_2Cl_2 (0.72 mL), DIPEA (50.6 mL, 0.291 mmol) and acetyl chloride (20.7 mL, 0.291 mmol) were added at 0 °C and the reaction mixture was stirred for 4 h at 23 °C. Then, the solution was diluted with CH_2Cl_2 (10 mL), and washed successively with 0.1 N HCl (5 mL), and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex: EtOAc 1:2) to afford **190** (27 mg, 25%) as a white solid.

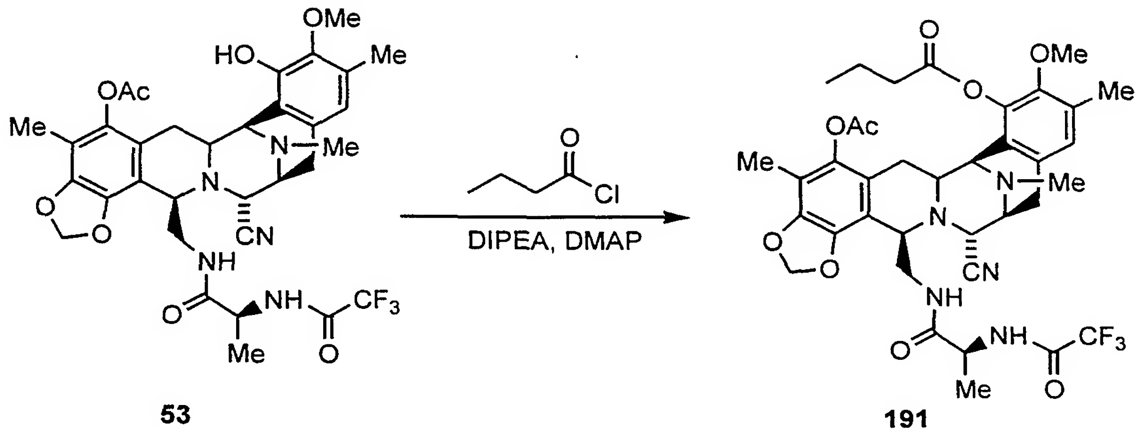
Rf = 0.24 Hex:EtOAc 1:1.

^{1}H NMR (300MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.02 (d, J = 0.9 Hz, 1H), 5.92 (d, J = 0.9 Hz, 1H), 5.30 (bs, 1H), 4.14 (d, J = 2.7 Hz, 1H), 4.10 (s, 1H), 3.90-3.73 (m, 2H), 3.68 (s, 3H), 3.67 (bs, 1H), 3.49 (bs, 1H), 3.42 (brd, J = 8.1 Hz, 1H), 3.24-3.20 (m, 1H), 3.01 (dd, J_1 = 8.4 Hz, J_2 = 18.3 Hz, 1H), 2.78 (d, J = 18 Hz, 1H), 2.64 (brd, J = 15.6Hz, 1H), 2.36 (s, 3H), 2.34 (s, 3H), 2.24 (s, 3H), 2.20 (s, 3H), 2.02 (s, 3H), 1.77 (dd, J_1 = 11.7 Hz, J_2 = 15.6 Hz, 1H), 0.65 (d, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 168.6, 168.1, 167.6, 147.9, 144.9, 142.8, 140.5, 131.5, 131.0, 127.7, 123.2, 120.3, 117.5, 112.3, 112.2, 101.7, 60.4, 59.0, 57.4, 57.2, 55.2, 54.9, 48.6, 41.5, 39.1, 36.6, 29.7, 26.7, 24.6, 20.7, 20.2, 17.6, 15.5, 9.2.

ESI-MS m/z: Calcd. for $C_{35}H_{38}F_3N_5O_9$: 729.70. Found $(M+1)^+$: 730.3.

Example 153



To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL). DIPEA (151.9 mL, 0.87 mmol), butyryl chloride (90.6 mL, 0.87 mmol) and DMAP (2.70 mg, 0.02 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 4h.. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 4:1) to afford **191** (20.2 mg, 12%) as a white solid.

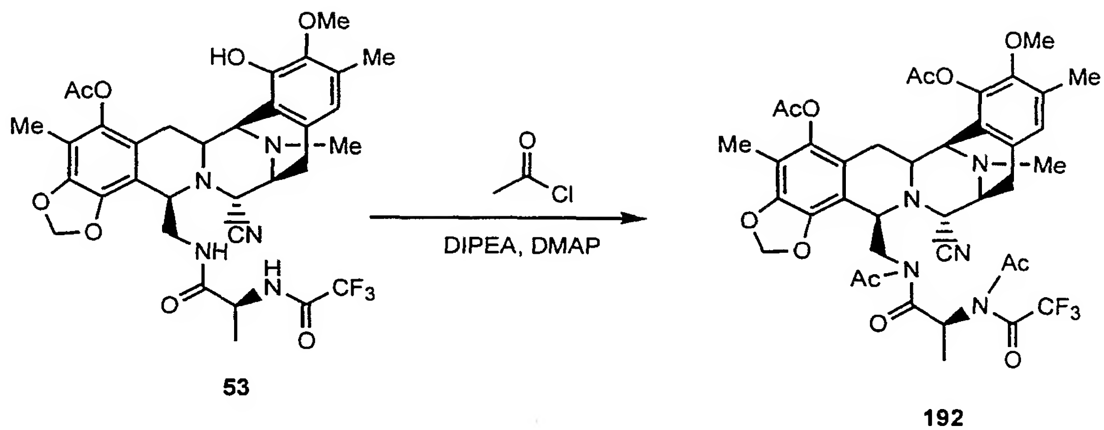
Rf = 0.3 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.03 (d, J = 1.2 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.16 (t, J = 5.4 Hz, 1H), 4.13 (d, J = 2.1 Hz, 1H), 4.10 (bs, 1H), 3.87-3.82 (m, 1H), 3.80-3.74 (m, 1), 3.68 (s, 3H), 3.64 (d, J = 3 Hz, 1H), 3.52-3.47 (m, 1H), 3.42 (brd, J = 7.2 Hz, 1H), 3.24-3.20 (m, 1H), 3.02 (dd, J_1 = 8.1 Hz, J_2 = 18.3 Hz, 1H), 2.77 (d, J = 17.7 Hz, 1H), 2.64 (brd, J = 16.2 Hz, 1H), 2.58 (t, J = 7.2 Hz, 2H), 2.33 (s, 3H), 2.25 (s, 3H), 2.22 (s, 3H), 2.02 (s, 3H), 1.87-1.73 (m, 3H), 1.08 (t, J = 7.2 Hz, 3H), 0.68 (d, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 172.1, 170.4, 157.8, 150.0, 146.9, 144.8, 142.6, 142.5, 133.3, 132.8, 129.6, 125.3, 122.3, 119.5, 118.4, 115.7, 114.3, 114.2, 103.8, 62.4, 61.0, 59.4, 59.2, 57.2, 57.0, 50.6, 43.6, 41.2, 38.1, 31.7, 28.7, 26.6, 22.2, 20.6, 19.7, 17.5, 15.7, 11.2.

ESI-MS m/z: Calcd. for $C_{37}H_{42}F_3N_5O_9$: 757.75. Found: 758.5 $(M+1)^+$, 780.5 $(M+23)^+$.

Example 154



To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (151.9 mL, 0.87 mmol), acetyl chloride (62.0 mL, 0.87 mmol) and DMAP (2.70 mg, 0.02 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 5 h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **192** (111 mg, 62%) as a white solid.

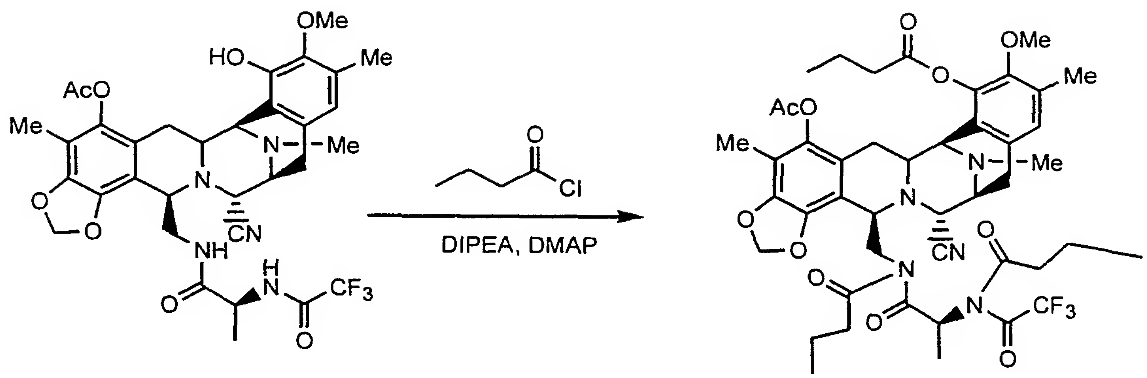
Rf = 0.25 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 5.87 (s, 1H), 5.81 (s, 1H), 4.70 (dd, J_1 = 2.4 Hz, J_2 = 9.9 Hz, 1H), 4.20 (d, J = 6.3 Hz, 1H), 4.09 (s, 1H), 3.74 (s, 3H), 3.60 (s, 1H), 3.28 (d, J = 7.5 Hz, 1H), 3.17 (d, J = 12 Hz, 1H), 3.07 (dd, J_1 = 7.2 Hz, J_2 = 18.3 Hz, 1H), 2.93 (d, J = 13.2 Hz, 1H), 2.66 (d, J = 15.3 Hz, 1H), 2.53 (d, J = 17.7 Hz, 1H), 2.47-2.20 (m, 1H), 2.37 (s, 1H), 2.33 (s, 3H), 2.26 (s, 3H), 2.24 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.96 (s, 3H), 1.72 (t, J = 14.4 Hz, 1H), 1.53 (d, J = 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 174.1, 168.6, 168.4, 167.5, 147.7, 144.8, 142.2, 140.4, 131.1, 130.5, 126.9, 123.3, 120.4, 117.5, 112.4, 111.8, 101.1, 60.7, 60.6, 57.6, 57.2, 56.6, 55.3, 52.7, 48.3, 41.5, 31.6, 29.7, 26.4, 25.5, 23.0, 22.6, 20.7, 20.5, 20.2, 17.8, 15.9, 14.1, 9.5.

ESI-MS m/z: Calcd. for $C_{39}H_{42}F_3N_5O_{11}$: 813.7. Found $(M+1)^+$: 814.3.

Example 155



53 193

To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (151.9 mL, 0.87 mmol), butyryl chloride (90.6 mL, 0.87 mmol) and DMAP (2.70 mg, 0.02 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 4h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 4:1) to afford **193** (58 mg, 30%) as a white solid.

Rf = 0.38 Hex:EtOAc 1:1.

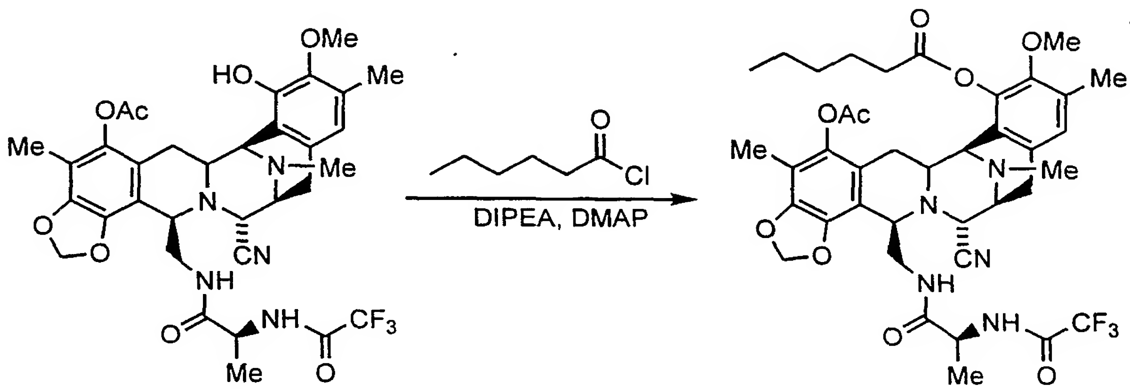
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.85 (s, 1H), 5.99 (d, J= 1.2 Hz, 1H), 5.90 (d, J= 1.2 Hz, 1H), 5.47-5.42 (m, 2H), 4.09-4.08 (m, 2H), 3.69 (s, 3H), 3.66 (m, 1H), 3.41 (d, J= 7.5 Hz, 1H), 3.28-3.18 (m, 2H), 3.07 (dd, J_1 = 8.1 Hz, J_2 = 18 Hz, 1H), 2.66 (d, J= 18.6 Hz, 1H), 2.61-2.39 (m, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.21 (s, 3H), 2.01 (s, 3H), 1.95-1.79 (m, 6H), 1.72-1.59 (m, 6H) 1.09 (t, J= 7.5 Hz, 3H), 0.99-0.94 (m, 6H), 0.85 (d, J= 6.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.7, 169.1, 168.4, 148.1, 145.0, 142.7, 140.9, 140.6, 131.2, 130.5, 128.4, 123.4, 119.9, 117.6, 113.0, 112.1, 101.9, 60.7, 59.5, 57.6, 56.5, 55.7, 55.2, 41.8, 41.4, 36.3, 35.8, 29.9, 27.0, 25.3, 20.5, 20.0, 18.8, 18.3, 15.8, 14.0, 13.8, 13.4,

12.7, 9.6.

ESI-MS m/z: Calcd. for $C_{45}H_{54}F_3N_5O_{11}$: 897.93. Found $(M+1)^+$: 898.3.

Example 156



53 194

To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (151.9 mL, 0.87 mmol), hexanoyl chloride (121.9 mL, 0.87 mmol) and DMAP (2.70 mg, 0.02 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 4h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 4:1) to afford **194** (37.5 mg, 22%) as a white solid.

Rf = 0.32 Hex:EtOAc 1:1.

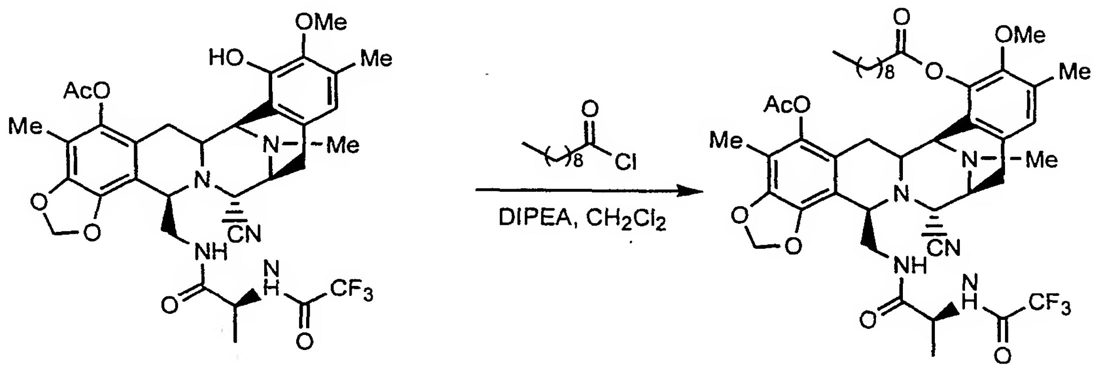
^1H NMR (300 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.02 (d, J = 1.2 Hz, 1H), 5.92 (d, J = 1.2 Hz, 1H), 5.22 (t, J = 5.7 Hz, 1H), 4.13 (d, J = 2.4 Hz, 1H), 4.09 (s, 1H), 3.88-3.81 (m, 1H), 3.80-3.71 (m, 1H), 3.67 (s, 3H), 3.64 (d, J = 3 Hz, 1H), 3.52-3.43 (m, 1H), 3.41 (brd, J = 6.6 Hz, 1H), 3.23-3.19 (m, 1H), 3.00 (dd, J_1 = 8.7 Hz, J_2 = 18.6 Hz, 1H) , 2.77 (d, J = 18Hz, 1H), 2.67-2.56 (m, 3H), 2.33 (s, 3H), 2.24 (s, 3H), 2.22 (s, 3H), 2.01 (s, 3H), 1.82-1.74 (m, 4H), 1.43-1.38 (m, 3H), 0.97-0.88 (m, 3H), 0.67 (d, J = 6.9Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 168.6, 148.2, 145.1, 143.0, 140.8, 140.7, 131.7,

131.1, 127.8, 123.5, 120.6, 117.7, 112.5, 102.0, 60.7, 59.2, 57.6, 57.4, 55.4, 55.2, 48.9, 41.8, 34.4, 31.8, 31.6, 29.9, 26.9, 25.0, 24.8, 22.9, 22.5, 20.4, 17.9, 15.8, 14.3, 14.1, 9.5.

ESI-MS m/z: Calcd. for $C_{39}H_{46}F_3N_5O_9$: 785.81. Found: 786 $(M+1)^+$, 805.5 $(M+23)^+$.

Example 157



53 195

To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (75.9 mL, 0.436 mmol), and decanoyl chloride (92.7mL, 0.436 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 4h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL), and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **195** (75 mg, 41%) as a white solid.

Rf = 0.32 Hex:EtOAc 1:1.

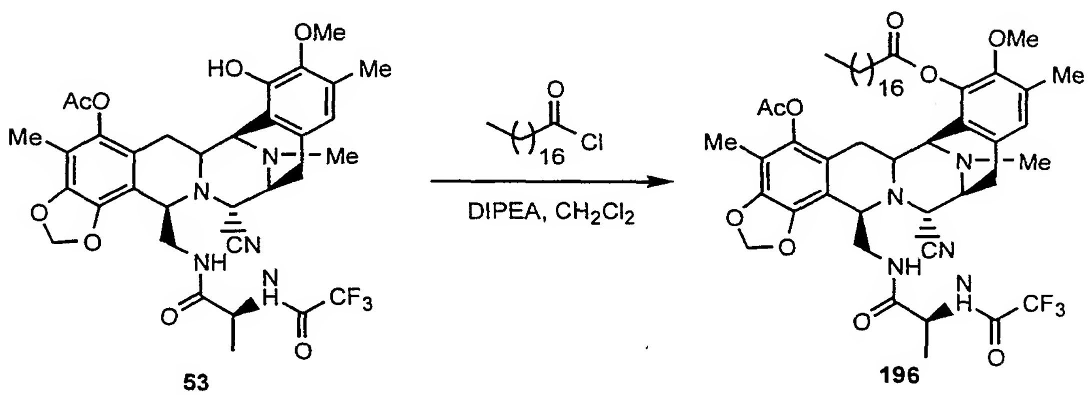
^{1}H NMR (300 Hz, $CDCl_3$) δ 6.82 (s, 1H), 6.03 (d, J = 1.5 Hz, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.26 (bs, 1H), 4.15 (s, 1H), 4.11 (s, 1H), 3.89-3.75 (m, 2H), 3.68 (s, 3H), 3.65 (bs, 1H), 3.52-3.44 (m, 1H), 3.43 (d, J = 8.1 Hz, 1H), 3.22 (brd, J = 11.4 Hz, 1H), 3.03 (dd, J_1 = 7.8 Hz, J_2 = 17.4 Hz, 1H), 2.78 (d, J = 17.7 Hz, 1H), 2.69-2.56 (m, 3H), 2.34 (s, 3H), 2.26 (s, 3H), 2.23 (s, 3H), 2.03 (s, 3H), 1.83-1.74 (m, 3H), 1.83-1.74 (m, 12H), 0.90-8.88 (m, 3H), 0.68 (d, J = 6 Hz, 3H).

^{13}C NMR (75 Hz, $CDCl_3$) δ 171.0, 170.1, 168.4, 148.0, 144.8, 142.8, 140.5, 131.5, 130.8, 127.5, 123.3, 120.3, 117.5, 112.3, 112.2, 101.7, 60.4, 59.0, 57.4, 57.2, 55.1, 55.0, 48.6, 41.5,

39.1, 34.2, 31.8, 29.4, 29.2, 26.7, 25.0, 24.6, 22.6, 20.2, 17.6, 15.5, 14.0, 9.2.

ESI-MS m/z: Calcd. for $C_{43}H_{54}F_3N_5O_9$: 841.91. Found $(M+1)^+$: 842.3.

Example 158



To a solution of **53** (150 mg, 0.218 mmol) in CH_2Cl_2 (1.09 mL), DIPEA (75.9 mL, 0.436 mmol), and stearoyl chloride (147.3 mL, 0.436 mmol) were added at 0 °C and the reaction mixture was stirred at 23 °C for 4h. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (RP-18, CH_3CN: H_2O 1:1) to afford **196** (86 mg, 41%) as a white solid.

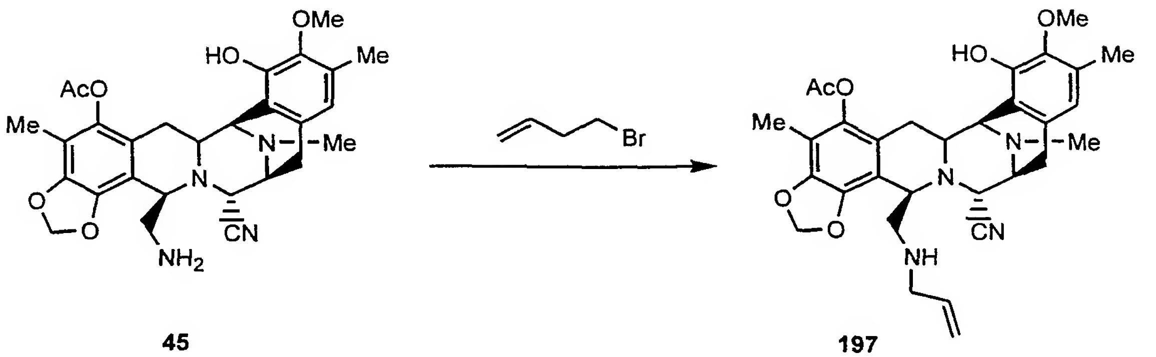
Rf = 0.42 Hex:EtOAc 1:1.

^1H NMR (300 MHz, $CDCl_3$) δ 6.81 (s, 1H), 6.03 (s, 1H), 5.92 (s, 1H), 5.21 (bs, 1H), 4.14 (s, 1H), 4.10 (s, 1H), 3.88-3.74 (m, 2H), 3.67 (s, 3H), 3.64 (d, J = 3 Hz, 1H), 3.49 (brd, J = 14.7 Hz, 1H), 3.42 (d, J = 8.1 Hz, 1H), 3.22 (brd, J = 11.4 Hz, 1H), 3.02 (dd, J_1 = 8.7 Hz, J_2 = 18.6 Hz, 1H), 2.78 (d, J = 18Hz, 1H), 2.68-2.56 (m, 3H), 2.33 (s, 3H), 2.25 (s, 3H), 2.02 (s, 3H), 1.82-1.73 (m, 3H), 1.42-1.19 (m, 28H), 0.87 (t, J = 7.2 Hz, 3H), 0.67 (d, J = 6.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 170.2, 168.5, 147.9, 144.8, 142.8, 140.4, 131.4, 130.9, 127.5, 123.3, 120.4, 117.5, 112.4, 112.1, 101.7, 60.4, 58.9, 57.4, 57.2, 55.2, 55.0, 48.6, 41.5, 39.0, 34.2, 31.9, 29.7, 29.6, 29.4, 29.3, 29.2, 26.7, 25.1, 24.6, 22.7, 20.2, 17.6, 15.5, 14.1,

9.2. ESI-MS m/z: Calcd. for $C_{51}H_{70}F_3N_5O_9$: 953.5. Found $(M+1)^+$: 954.4.

Example 159



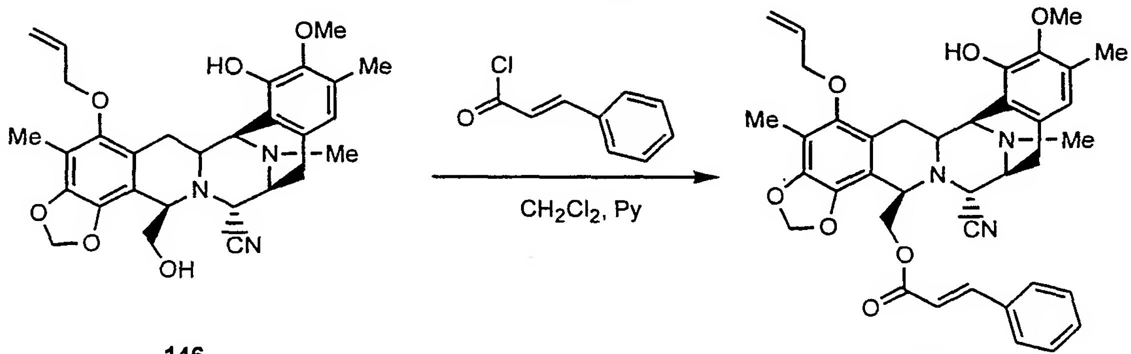
To a solution of **45** (10 mg, 0.019 mmol) in CH_2Cl_2 (0.095 mL), triethylamine (2.94 mL, 0.021 mmol) and allyl bromide (2.0 mL, 0.023 mmol) were added at 23 °C. The reaction mixture was stirred for 6 h and then, the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (SiO_2, MeOH: EtOAc 1:5) to afford **197** (3.8 mg, 35%) as a white solid.

Rf = 0.19 EtOAc:MeOH 5:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.43 (s, 1H), 5.95 (s, 1H), 5.89 (s, 1H), 5.62-5.59 (m, 1H), 4.94-4.84 (m,, 2H), 4.19 (s, 1H), 4.08 (s, 1H), 3.98 (t, J = 4.5 Hz, 1H), 3.76 (s, 3H), 3.32-3.26 (m, 2H), 3.07 (dd, J_1 = 7.5 Hz, J_2 = 17.4 Hz, 1H), 2.89 (d, J = 6 Hz, 2H), 2.80 (d, J = 3.9 Hz, 1H), 2.76 (d, J = 3.3 Hz, 1H), 2.57-2.52 (m, 2H), 2.33 (s, 6H), 2.24 (s, 3H), 1.99 (s, 3H), 1.88-1.79 (dd, J_1 = 12.9 Hz, J_2 = 15.9 Hz, 1H).

ESI-MS m/z: Calcd. for $C_{31}H_{36}N_4O_6$: 560.64. Found $(M+1)^+$: 561.3.

Example 160



146

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To a solution of 146 (50 mg, 0.096 mmol) in CH_2Cl_2 (0.96 mL), pyridine (11.7 mL, 0.144 mmol), and cinnamoyl chloride (24.0 mg, 0.144 mmol) were added at 23 °C and the reaction mixture was stirred for 18 h at that temperature. Then, the solution was diluted with CH_2Cl_2 (10 mL) and washed successively with 0.1 N HCl (5 mL) and a solution of 10% $NaHCO_3$ (5 ml). The organic layer was dried over Na_2SO_4, filtered, and the solvent was eliminated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, Hex:EtOAc 1:2) to afford **198** (54 mg, 86%) as a white solid.

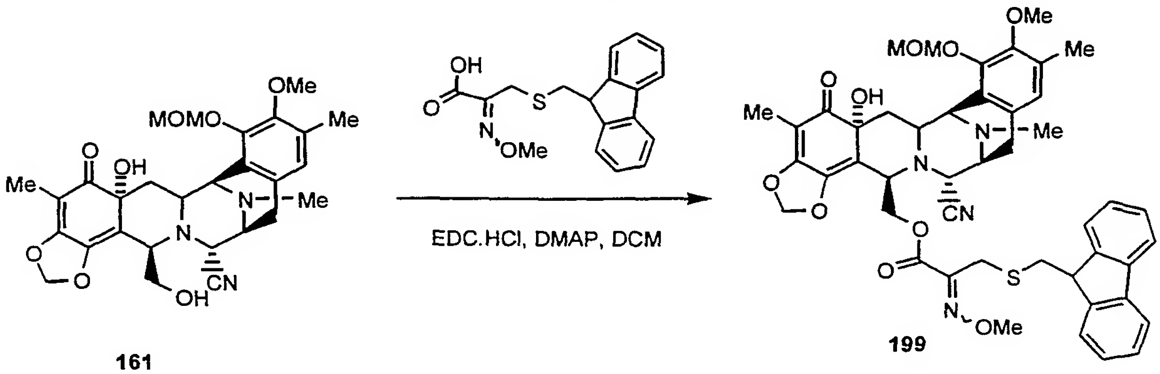
Rf = 0.45 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.37 (m, 6H), 6.38 (s, 1H), 6.19-6.03 (m, 1H), 6.08 (d, J = 15.9 Hz, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.88 (d, J = 1.5 Hz, 1H), 5.62 (s, 1H), 5.38 (dd, J_1 = 1.5 Hz, J_2 = 17.1 Hz, 1H), 5.26 (dd, J_1 = 1.5 Hz, J_2 = 10.5 Hz, 1H), 4.47 (dd, J_1 = 3.6 Hz, J_2 = 10.8 Hz, 1H), 4.23-4.11 (m, 5H), 3.89 (dd, J_1 = 4.8 Hz, J_2 = 11.1 Hz, 1H), 3.51 (s, 3H), 3.34 (brd, J = 8.4 Hz, 1H), 3.27-3.21 (m, 2H), 2.97 (dd, J_1 = 7.8 Hz, J_2 = 17.7 Hz, 1H), 2.28 (s, 3H), 2.15 (s, 3H), 2.04 (s, 3H), 1.91 (dd, J_1 = 12 Hz, J_2 = 15.6 Hz, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 166.5, 148.8, 146.7, 144.7, 144.5, 142.7, 139.5, 134.4, 134.1, 131.1, 130.6, 129.1, 128.7, 128.2, 121.9, 121.2, 118.5, 117.8, 116.8, 112.9, 112.7, 101.5, 74.7, 65.2, 60.7, 60.6, 57.4, 56.8, 56.6, 55.7, 41.9, 31.8, 26.7, 25.5, 22.9, 15.9, 14.4, 9.7.

ESI-MS m/z: Calcd. for $C_{38}H_{39}N_3O_7$: 649.7. Found $(M+1)^+$: 650.3.

Example 161



161

199

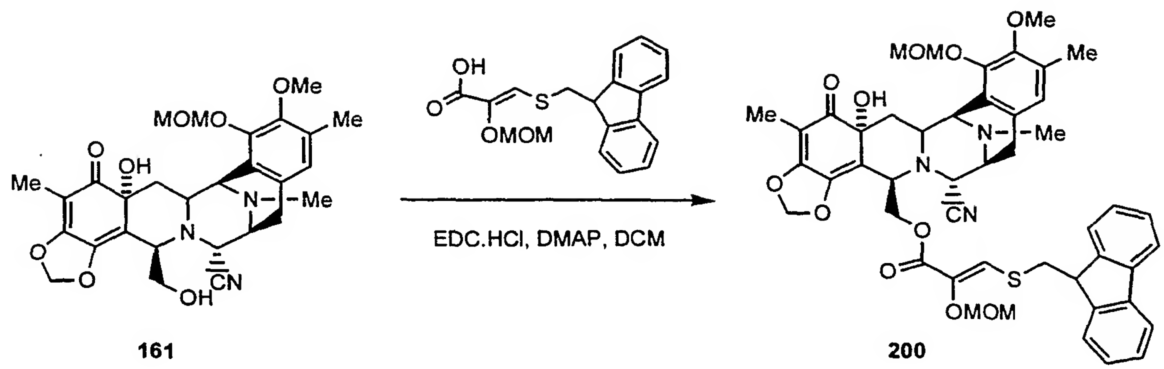
To a solution of 161 (78.5 mg, 0.146 mmol) and the cysteine derivative (81.1 mg, 0.247 mmol) in anhydrous CH2Cl2 (7.3 mL), DMAP (50 mg, 0.41 mmol) and EDC.HCl (78.1 mg, 0.41 mmol) were added at 23 oC. The reaction mixture was stirred at 23 oC under Argon atmosphere for 1.5 h. The mixture was diluted with CH2Cl2 (20 mL) and extracted with an aqueous saturated solution of sodium bicarbonate (25 mL). The aqueous phase was extracted with additional CH2Cl2 (20 mL) and the combined organic extracts were dried over Na2SO4, filtered and the solvent was eliminated under reduced pressure. The crude of the reaction was purified by flash column chromatography (inner diameter of the column 2 cm, height of silica 10 cm) with mixtures of ethyl acetate/hexane in a gradient manner, from 1:4 to 3:1 as eluent. Compound 199 (113 mg, 88%) was obtained as a pale yellow solid.

Rf= 0.36 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.76 (d, J = 7.8 Hz, 2H), 7.63 (d, J = 7.8 Hz, 2H), 7.40 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.6 Hz, 2H), 6.54 (s, 1H), 5.80 (s, 1H), 5.74 (s, 1H), 5.10 (d, J = 5.7 Hz, 1H), 5.08 (d, J = 5.7 Hz, 1H), 4.50 (dd, J = 4.9 Hz, J = 11.8 Hz, 1H), 4.20-4.05 (m, 4H), 4.02 (s, 3H), 3.81 (s, 3H), 3.61 (d, J = 13.8 Hz, 1H), 3.55 (d, J = 13.8 Hz, 1H), 3.50 (s, 3H), 3.21 (m, 1H), 3.06 (m, 1H), 3.00 (d, J = 6.0 Hz, 2H), 2.90 (dd, J = 8.9 Hz, J = 17.4 Hz, 1H), 2.79 (s, 1H), 2.56 (m, 1H), 2.50 (dd, J = 4.8 Hz, J = 14.9 Hz, 1H), 2.21 (s, 3H), 2.18 (s, 3H), 1.80 (s, 3H), 1.75 (m, 2H).

ESI-MS m/z: Calcd. for $C_{46}H_{48}N_4O_{10}S$: 848.3. Found: 849.3 $(M+1)^+$, 871.3 $(M+23)^+$. HPLC: Conditions: Column: Simmetry C18, Mobile phase: CH_3CN/H_2O in gradient from 50 to 100% in 25 minutes. ∅ = 1 mL/min, t= 40 °C. Retention time: 16.04 minutes. HPLC purity in area: 89.29%.

Example 162



To a solution of **161** (80 mg, 0.148 mmol) and the cysteine derivative (76 mg, 0.223 mmol) in anhydrous CH_2Cl_2 (6.8 mL), DMAP (45 mg, 0.37 mmol) and EDC.HCl (71 mg, 0.37 mmol) were added at 23 °C. The reaction mixture was stirred at 23 °C under Argon atmosphere for 2.5 h Then, the mixture was diluted with CH_2Cl_2 (20 mL) and extracted with an aqueous saturated solution of sodium bicarbonate (25 mL). The aqueous phase was extracted with additional CH_2Cl_2 (20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. The crude of the reaction was purified by flash column chromatography (inner diameter of the column 2 cm, height of silica 10 cm) with mixtures of ethyl acetate/hexane in gradient from 1:4 to 3:1 as eluent. Compound **200** (83 mg, 65%) was obtained as a pale yellow solid.

Rf = 0.5 Hex:EtOAc 1:1.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (m, 3H), 7.49 (d, J = 7.3 Hz, 1H), 7.36 (t, *J* = 7.3 Hz, 2H), 7.32- 7.23 (m, 2H), 6.65 (s, 1H), 5.80 (s, 1H), 5.79 (s, 1H), 5.13 (d, *J* = 6.1 Hz, 1H), 5.11 (d, *J* = 6.1 Hz, 1H), 5.05 (d, *J* = 6.1 Hz, 1H), 5.01 (d, *J* = 6.3 Hz, 1H), 4.76 (dd, *J* = 3.9 Hz, *J* = 11.9 Hz, 1H), 4.15- 4.03 (m, 4H), 3.96 (t, *J* = 4.0 Hz, 1H), 3.87 (s, 3H), 3.55 (s, 3H), 3.51 (s, 3H), 3.34-3.29 (m, 2H), 3.24 (dd, *J* = 5.5 Hz, *J* = 13.5 Hz, 1H), 3.03 (m, 1H), 2.97 (t, *J* = 7.5 Hz, 1H), 2.44-2.35 (m, 3H), 2.29 (s, 3H), 2.14 (s, 3H), 1.98 (dd, *J* = 8.06, *J* = 15.1 Hz, 2H), 1.75 (s, 3H).

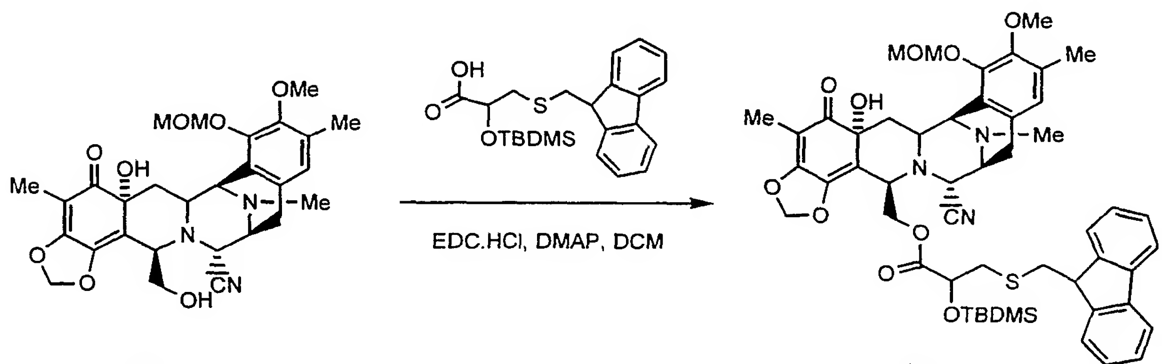
^{13}C NMR (75 MHz, $CDCl_3$) δ 196.98, 161.13, 158.21, 149.01, 148.78, 145.05, 144.91, 141.01, 140.69, 140.07, 137.53, 132.76, 131.15, 129.41, 127.70, 127.67, 127.21, 126.83, 125.28, 125.05, 124.94, 122.51, 119.84, 119.73, 116.61, 110.26, 104, 57, 101.40, 99.23,

96.70, 70.25, 63.15, 60.40, 58.89, 57.52, 56.98, 56.72, 56.15, 55.06, 47.22, 41.37, 38.26, 35.22, 29.57, 25.34, 15.62, 7.26.

ESI-MS m/z: Calcd. for $C_{47}H_{49}N_3O_{11}S$: 863.97. Found: 865.0 $(M+1)^+$, 887.1 $(M+23)^+$.

HPLC: Conditions: Column: Simmetry C18, Mobile phase: CH_3CN/H_2O in gradient from 50 to 100% in 25 minutes. ∅ = 1 mL/min, t= 40 °C. Retention time: 15.36 minutes. HPLC purity in area: 91.56%.

Example 163



161 201

To a solution of **161** (418 mg, 0.77 mmol) and the cysteine derivative (321 mg, 0.77 mmol) in anhydrous CH_2Cl_2 (35 mL), DMAP (235 mg, 1.92 mmol) and EDC.HCl (369 mg, 1.92 mmol) were added at 23 °C and the reaction was stirred under Argon atmosphere for 2 h. The mixture was diluted with CH_2Cl_2 (20 mL) and extracted with an aqueous saturated solution of sodium bicarbonate (25 mL). The aqueous phase was extracted with additional CH_2Cl_2 (20 mL) and the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. The crude of the reaction was purified by flash column chromatography (inner diameter of the column 3 cm, height of silica 11 cm) with mixtures of ethyl acetate/hexane in a gradient manner, from 1:3 to 3:1 as eluent. Compound **201** (372 mg, 52%) was obtained as a pale yellow solid.

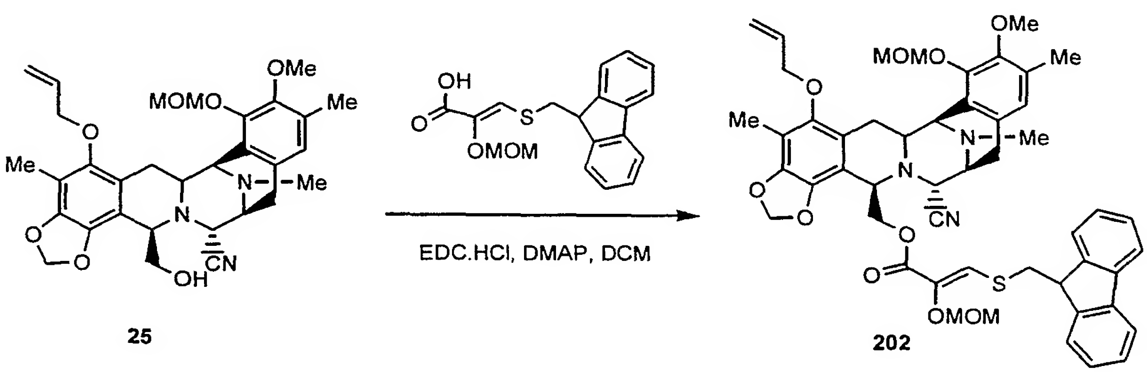
Rf = 0.41 Hex:EtOAc 1:1.

^{1}H-RMN ($CDCl_3$, 300 MHz) δ 7.76-7.64 (m, 4H), 7.41-7.30 (m, 4H), 6.54 (s, 1H major isomer), 6.51 (s, 1H, minor isomer), 5.69 (s, 1H, minor isomer), 5.67 (s, 1H, major isomer),

5.60 (s, 1H minor isomer), 5.57 (s, 1H major isomer), 5.08 (s, 2H), 4.26 (t, J = 5.1 Hz, 1H minor isomer), 4.23 (t, J = 4.9 Hz, 1H major isomer), 4.07-4.03 (m, 3H), 3.98- 3.88 (m, 3H), 3.84 (s, 3H), 3.71 (dt, J_1 = 5.6 Hz, J_2 = 10.0 Hz, 1H), 3.49 (s, 3H, major isomer), 3.49 (s, 3H, minor isomer), 3.40 (dt, J_1 = 5.6 Hz, J_2 = 9.5 Hz, 1H), 3.18 (m, 3H), 3.11 (m, 1H), 2.91-2.82 (m, 1H), 2.48-2.28 (m, 2H), 2.24 (s, 3H), 2.16 (s, 3H, major isomer), 2.14 (s, 3H, minor isomer), 2.03 (s, 3H), 1.91 (dt, J_1 = 8.8 Hz, J_2 = 14.4 Hz, 1H), 1.76 (s, 3H, minor isomer), 1.76 (s, 3H major isomer), 0.85 (s, 9H minor isomer), 0.85 (s, 9H major isomer), 0.04 and 0.01 (s, 6H both isomers).

ESI-MS m/z: Calcd. for $C_{51}H_{61}N_3O_{10}SSi$: 935.4. Found: 936.4 $(M+1)^+$, 958.3 $(M+23)^+$.

Example 164



25

202

To a solution of **25** (2 mg, 0.0035 mmol) and an excess amount of the cysteine derivative in anhydrous CH_2Cl_2 (0.2mL), an excess amounts of DMAP and EDC.HCl were added at 23 °C. The reaction mixture was stirred at 23 °C under Argon atmosphere for 14 h. Then, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous phase was extracted with additional CH_2Cl_2 (10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. The crude of the reaction was purified by flash column chromatography (SiO_2, Hex:EtOAc 4:1) to afford **202** as a pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) (poor resolution) δ 7.78.7,62 (m, 4H), 7.41-7.26 (m, 4H), 6.73 (s, 1H), 6.10 (m, 1H), 5.92 (d, J = 1.3 Hz, 1H), 5.88 (d, J = 1.3 Hz, 1H), 5.40-5.22 (m, 2H),

5.11 (s, 3H), 5.02 (d, J = 13.8 Hz, 1H), 4.29-4.02 (m, 6H), 3.97 (m, 1H), 3.72 (d, J = 12.5 Hz, 2H), 3.70 (s, 3H), 3.58 (s, 3H), 3.51 (d, J = 12.3 Hz, 2H), 3.50 (s, 3H), 3.49-3.20 (m, 4H), 2.54-2.28 (m, 4H), 2.40 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H).

Fermentation Procedures

Example A

Seed medium YMP3 containing 1% glucose; 0.25% beef extract; 0.5% bacto-peptone; 0.25% NaCl; 0.8% $CaCO_3$ was inoculated with 0.1% of a frozen vegetative stock of the microorganism, strain A2-2 of *Pseudomonas fluorescens,* and incubated on a rotary shaker (250 rpm) at 27°C. After 30 h of incubation, the seed culture was added to a agitated-vessel fermentor with a production medium composed of 2% dextrose; 4% mannitol, 2% dried brewer's yeast (*Vitalevor® Biolux, Belgium*); 1% $(NH_4)_2SO_4$; 0.04% K_2HPO_4; 0.8 KCl; 0.001% $FeCl_3$; 0.1% L-Tyr; 0.8% CO_3Ca; 0.05% PPG-2000; 0.2% anti-foam silicone (ASSAF-100, RHODIA UK). The sterilisation was carried out at 122°C 30 minutes. The volume inoculated was a 2% (v/v). The temperature was 27°C (0 to 16h) and 24°C from 16h to final process (41 hours). The dissolve oxygen-pressure was upper to 25%. The pH was controlled at 6.0 with diluted sulphuric acid since 28 hours till final process. The overpressure was 0.5 bar. A 1% mannitol or sorbitol was added from 16 h to final process (for two days running) and 2% for three days fermentation-process.

After 41 or 64 hours, the fermentation broth must be extracted for recovery safracin B or KCN treatment in the clarified broth for recovery safracin B - cyano.

Example B

Obtention of safracin B cyano from the crude extract.

A clarification or filtration from the fermentation broth at pH 6 removes the solids. The clarified broth was adjusted a pH 9.5 with diluted sodium hydroxide and extracted twice with 2:1 (v/v) ethyl acetate, methylene chloride or butyl acetate. The extraction was carried out

into an agitated-vessel during 20', the temperature of the mixture was maintained at 8 to 10°C. The two phases were separated by a liquid-liquid centrifuge. The organic phase was dried with sodium sulphate anhydrous or frozen and then filtered for removing ice. This organic phase (ethyl acetate layer) was evaporated until obtention of an oil-crude extract.

Example C

Obtention of safracin B cyano from the clarified broth.

A clarification or filtration from the fermentation broth at pH 6 removes the solids. The clarified broth was adjusted at pH 3.9 with concentrated acetic acid. 0.5 grams per litre of KCN are added to the clarified broth an incubated at 20°C during 1 hour with agitation. Then, the temperature was decreased at 15°C and the pH was adjusted at 9.5 with diluted sodium hydroxide and extracted with 2:1.5 (v/v) ethyl acetate. The extraction was carried out into an agitated-vessel during 20 minutes, the temperature of the mixture was maintained at 8 to 10°C. The two phases were separated by a liquid-liquid centrifuge. The organic phase was dried with sodium sulphate anhydrous. This organic phase (ethyl acetate layer) was evaporated until obtention of an oil-crude extract. This extract was purified by flash column chromatography (SiO_2, gradient 20:1 to 10: to 5:1 ethyl acetate:methanol) to afford quantitatively compound 2 as a light yellow solid.

Rf: 0.55 (ethyl acetate:methanol5:1); .t_R= 19.9 min [HPLC, Delta Pack C4, 5μm, 300 A, 150x3 mm, λ=215 nm, flow= 0.7 ml/min, temp= 50°C, grad.: CH_3CN-aq. NaOAc (10mM) 85% - 70% (20')];

^{1}H NMR (300 Mhz, $CDCl_3$): δ 6.54 (dd, J_1 = 4.4Hz, J_2 = 8.4 Hz, 1H),6.44 (s, 1H), 4.12 (d, J = 2.4 Hz, 1H), 4.04 (d, J = 2.4 Hz, 1H), 4.00 (s, 3H), 3.87 (bs, 1H), 3.65 (ddd, J_1 = 1.5 Hz, J_2 = 8.7 Hz, J_3 = 9.9 Hz, 1H), 3.35 (br. D, J = 8.4 Hz, 1H), 3.15-2.96 (m, 4H), 2.92 (q, J = 7.2 Hz, 1H), 2.47 (d, J = 18.3 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H) 1.83 (s, 3H), 1.64 (ddd, J_1 = 2.7 Hz, J_2 = 11.1 Hz, J_3 = 14.1 Hz, 1H), 0.79 (d, J = 7.2 Hz, 3H);

^{13}C NMR (75 Mhz, $CDCl_3$): δ 186.0 (q), 175.9 (q), 156.2 (q), 146.8 (q), 142.8 (q), 140.7 (q), 136.6 (q), 130.5 (q), 128.8 (q), 127.0 (q), 120.5 (s), 117.4 (q), 116.5 (q), 60.8 (t), 60.4 (s),

58.7 (t), 56.2 (s), 55.7 (s), 54.8 (s), 54.8 (s), 54.4 (s), 50.0 (s), 41.6 (t), 39.8 (d), 25.2 (d), 24.4 (d), 21.2 (t), 15.5 (t), 8.4 (t).

ESI-MS m/z: Calcd for $C_{29}H_{35}N_5O_6$: 549.6. Found $(M+Na)^+$: 572.3.

Example D

A medium (50 l) composed of dextrose (2%), mannitol (4%), dry brewer's yeast (2%), ammonium sulphate (1%), potassium secondary phosphate (0.04%), potassium chloride (0.8%), iron (III) chloride 6-hydrate (0.001%), L-tyrosine (0.1%), calcium carbonate (0.8%), poly- (propylene glycol) 2000 (0.05%) and antifoam ASSAF 1000 (0.2%) was poured into a jar-fermentor with 75 l total capacity and, after sterilisation, inoculated with seed culture (2%) of A2-2 strain (FERM BP-14) and aerated cultivation under agitation was carried out at 27°C to 24°C for 64 hours (aeration of 75 l per minute and agitation from 350 to 500 rpm). The pH was controlled by automatic feeding of diluted sulphuric acid from 27 hours to final process. A 2% mannitol was added from 16 hours to final process. The cultured medium (45 l) thus obtained was, after removal of cells by centrifugation, adjusted to pH 9.5 with diluted sodium hydroxide, extracted with 25 litres of ethyl acetate twice. The mixture was carried out into an agitated-vessel at 8°C for 20 minutes. The two phases were separated by a liquid-liquid centrifuge. The organic phases were frozen at -20°C and filtered for removing ice and evaporated ice and evaporated until obtention of a 40 g oil-dark-crude extract. After introduction of the cyanide group and purification, 3.0 grams of safracin B cyano were obtained.

Example E

A medium (50 l) composed of dextrose (2%), mannitol (4%), dry brewer's yeast (2%), ammonium sulphate (1%), potassium secondary phosphate (0.02%, potassium chloride (0.2%), Iron (III) chloride 6-hydrate (0.001%, L-tyrosine (0.1%), calcium carbonate (0.8%, poly- (propylene glycol) 2000 (0.05%) and antifoam ASSAF 1000 (0.2%) was poured into a jar-fermentor with 75 l total capacity and, after sterilisation, inoculated with seed culture (2%) of A2-2 strain (FERM BP-14) and aerated cultivation under agitation was carried out at 27°C to 24°C for 41 hours (aeration of 75 l per minute and agitation from 350 to 500 rpm).

The pH was controlled by automatic feeding of diluted sulphuric acid from 28 hours to final process. A 1% mannitol was added from 16 hours to final process. The cultured medium (45 l) thus obtained was, after removal of cells by centrifugation, adjusted to pH 3.9 with 200 ml of conc. acetic acid. 25 grams of potassium cyanide 97% were added and after 1 hour of agitation at 20°C, the pH was adjusted to 9.5 with 1500 ml of a solution 10% sodium hydroxide. Then, extracted with 35 litres of ethyl acetate. The mixture was carried out into an agitated -vessel at 8°C for 20 minutes. The two phases were separated by a liquid-liquid centrifuge. The organic phase was dried by sodium sulphate anhydrous and evaporated until obtention of a 60 g oil-dark-crude extract.

After chromatography, 4.9 grams of safracin B cyano were obtained.

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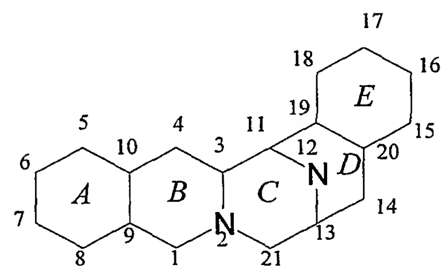
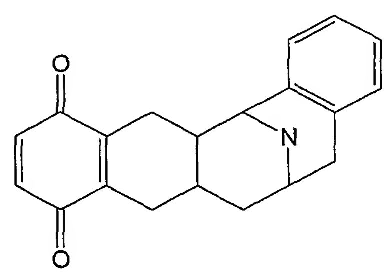
Claims

1. A compound with the five membered fused ring ecteinascidin structure of the formula (XIV):

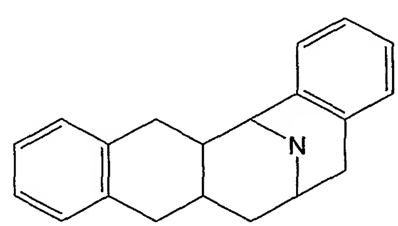


the compound lacking a 1,4-bridging group and having at the C-1 position a substituent selected from an optionally protected or derivatised aminomethylene group or an optionally protected or derivatised hydroxymethylene group.

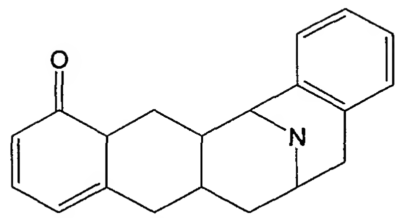
2. A compound according to claim 1, where the ring structure is of formula (a), (b) or (c):



(a)



(b) or



(c).

3. A compound according to claim 1 or 2, wherein the C-1 substituent is a hydrophobic group of moderate bulk.

4. A compound according to claim 1, 2 or 3, where the substituent at C-1 is an optionally protected or derivatised aminomethylene group.

5. A compound according to claim 4, where the C-1 substituent is a monosubstituted aminomethylene group.

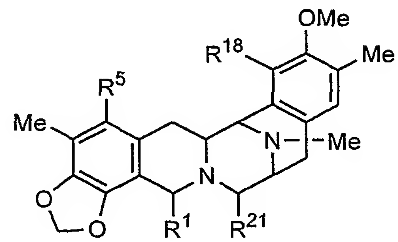
6. A compound according to claim 5, wherein the C-1 substituent is of the formula –CH_2-NH CO-R^a or –CH_2-NH CS-R^a.where R^a is alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, arylalkylene, haloalkylarylakylene, acyl, haloacyl, arlyalkyl, alkenyl and amino acid.

7. A compound according to claim 4, where the C-1 substituent is an optionally protected or derivatised hydroxymethylene group.

8. A compound according to claim 7, wherein the C-1 substituent is of the formula –CH_2-O CO-R^a.where R^a is alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, arylalkylene,

haloalkylarylakylene, acyl, haloacyl, arlyalkyl, alkenyl and amino acid.

9. A compound according to claim 1 of the formula:



wherein:

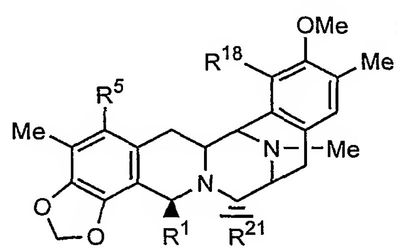
R^1 is $-CH_2-N(R^a)_2$ or $-CH_2-OR^a$, where R^a is H; alkyl-CO-; haloalkyl-CO-; cycloalkylalkyl-CO-; haloalkyl-O-CO-; arylalkyl-CO-; arylalkenyl-CO-; heteroaryl-CO-; alkenyl-CO-; alkenyl; amino acid acyl; or a protecting group;

R^5 is –OR", where R" is H; alkyl-CO-; cycloalkyl-CO-; haloalkyl-CO- or a protecting group;

R^{18} is -OR, where R is H, alkyl-CO-; cycloalkylalkyl-CO-; or a protecting group;

R^{21} is –CN or –OH.

10. A compound according to claim 9, which is of the formula:



wherein R^1, R^5, R^{18}, and R^{21} are as defined.

11. A compound according to claim 9 or 10, wherein R^1 is $-CH_2-NHR^a$.

12. A compound according to any of claims 9 to 11, wherein R^a is –aa-R^b where aa is amino acid acyl and R^b is as defined for R^a.

13. A compound according to claim 12, wherein the amino acid acyl is further substituted with one or more R^a groups.

14. A compound according to any of claims 9 to 13, wherein R^1 is $-CH_2$-NH-aa-R^b where aa is an amino acid and R^b is hydrogen; protecting group; arylalkenyl-CO-; haloalkyl-CO-; alkyl-CO-; arylalkyl-CO-; or amino acid acyl,

15. A compound according to claim 14, wherein R^1 is $-CH_2$-NH-aa-R^b where aa is alanine and R^b is hydrogen, Boc, PhNHCS-, CF_3CO-, PhNAcCS-, trifluorocinnamoyl, cinnamoyl, C_3F_7CO-, butyryl, 3-chloroproprionoyl, hydrocinnamoyl, hexanoyl, phenylacetyl, Cbz-val or acetyl; $-CH_2$-aa-R^b where aa is valine and R^b is Cbz or Boc; $-CH_2$-aa-R^b where aa is phenylalanine and R^b is Boc; $-CH_2$-aa-R^b where aa is proline and R^b is Boc; $-CH_2$-aa-R^b where aa is arginine and R^b is Boc; or $-CH_2$-aa-R^b where aa is tryptophan and R^b is Boc.

16. A compound according to any of claims 9 to 13, wherein R^1 is $-CH_2$-NR^a-aa-R^b where aa is an amino acid, R^a is alkyl-CO- and R^b is haloalkyl-CO-.

17. A compound according to claim 16, wherein R^1 is $-CH_2$-NR^a-aa-R^b where aa is acetylalanine, R^a is acetyl or butyryl, and R^b is CF_3-CO-.

18. A compound according to any of claims 9 to 13, wherein R^1 is $-CH_2$-NHR^a where R^a is hydrogen, protecting group, alkyl-CO-; alkenyl-CO-; arylalkenyl-CO-; arylalkyl-CO-; heteroaryl-CO-; cycloalkylalkyl-CO-; or alkenyl.

19. A compound according to claim 18, wherein R^1 is $-CH_2$-NHR^a where R^a is hydrogen, Troc, acetyl; isovaleroyl, decanoyl, cinnamoyl, hydrocinnamoyl, phenylacetyl, propionyl, myristoyl, stearoyl, hexanoyl, crotonyl, chloronicotinoyl, cyclohexylacetyl, cyclohexylpropionyl or allyl.

20. A compound according to any of claims 9 to 13, wherein R^1 is $-CH_2$-OR^a where R^a is hydrogen; a protected cysteine; a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C(NH$Prot^{NH}$)-CO-, where $Prot^{SH}$ and $Prot^{NH}$ are protecting groups for thiol and for amino; a protecting group; alkyl-CO-; arylalkyl-CO-; arylalkenyl-CO-; a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C(=NO$Prot^{OH}$)-CO- where $Prot^{SH}$ and $Prot^{OH}$ are protecting groups for thiol and for hydroxy; or a cysteine derivative of formula $Prot^{SH}$-S-CH=C(-O$Prot^{OH}$)-CO-, where $Prot^{SH}$ and $Prot^{OH}$ are protecting groups for thiol and for hydroxy.

21. A compound according to claim 20, wherein R^1 is $-CH_2$-OR^a where R^a is hydrogen; S-Fm-O-TBDMS-cysteine;a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C(NH$Prot^{NH}$)-CO-, where $Prot^{SH}$ is Fm and $Prot^{OH}$ is Troc; TBDPS; butyryl; trfiluormethylcinnamoyl; cinnamoyl; hydrocinnamoyl; a cysteine derivative of the formula $Prot^{SH}$-S-CH_2-C(=NO$Prot^{OH}$)-CO- where $Prot^{SH}$ is Fm and $Prot^{OH}$ is methoxy; or a cysteine derivative of formula $Prot^{SH}$-S-CH=C(-O$Prot^{OH}$)-CO-, where $Prot^{SH}$ is Fm and $Prot^{OH}$ is MOM.

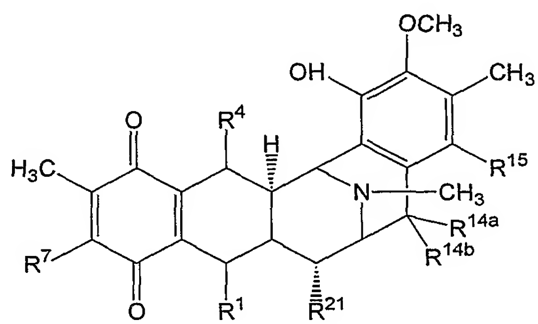
22. A compound according to any of claims 9 to 21, wherein R^5 is –OR", where R" is H; alkyl-CO where the alkyl has an odd number of carbon atoms, ω-cyclohexylalkyl-CO-; or a protecting group;

23. A compound according to any of claims 9 to 22, wherein R^{18} is -OR, where R is H, alkyl-CO-; or a protecting group;

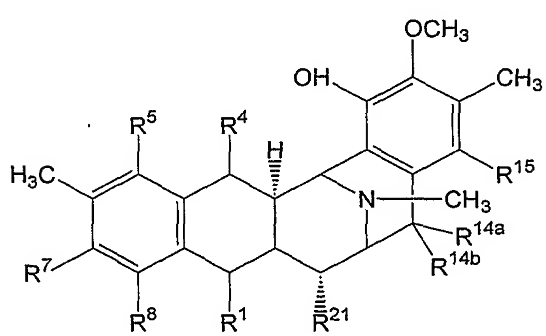
24. A compound according to any of claims 9 to 22, wherein R^{21} is –CN.

25. A compound according to any of claims 9 to 22, wherein R^{21} is –OH.

26. A compound according to claim 1, which is of the formula (XVIIa):



or formula (XVIIb):



where

R^1 is an optionally protected or derivatised aminomethylene group, or an optionally protected or derivatised hydroxymethylene group;

R^4 is -H;

R^5 is -H or -OH;

R^7 is $-OCH_3$ and R^8 is -OH or R^7 and R^8 together form a group $-O-CH_2-O-$;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group; and

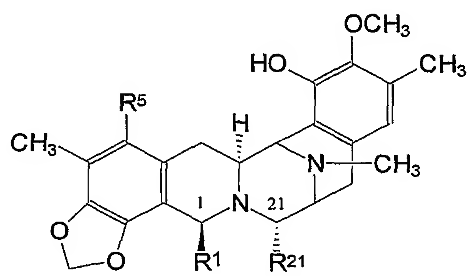
R^{15} is -H or -OH;

R^{21} is -H, -OH or -CN;

and derivatives.

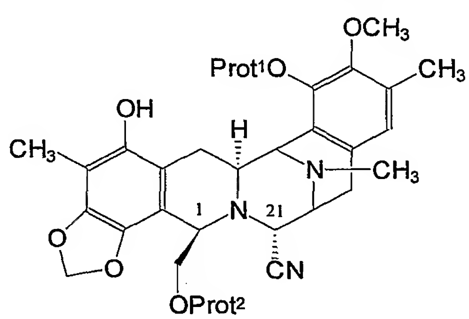
27. A compound according to claim 26, where R^5 is acetyloxy or other acyloxy group of up to 4 carbon atoms.

28. A compound according to claim 1, of the general formula (XX):



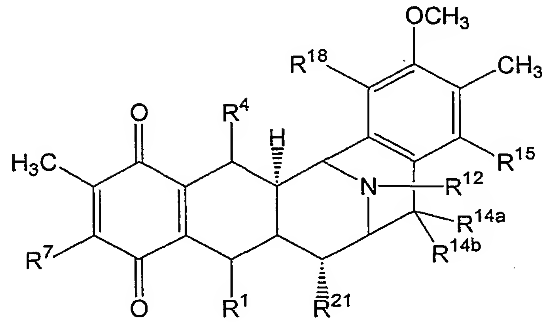
where R^1 is a monosubstituted amidomethylene group; R^5 is a small oxy-sidechain; and R^{21} is a cyano group or a hydroxy group.

29. A compound according to claim 1, of the general formula (XXI):

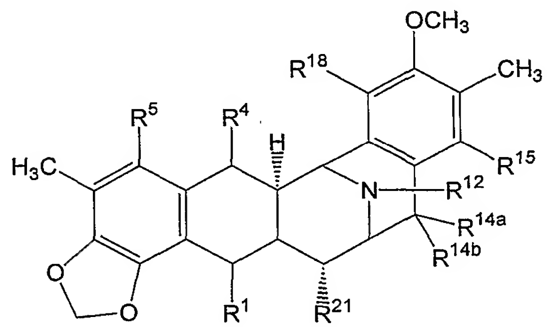


where $Prot^1$ and $Prot^2$ are hydroxy protecting groups, preferably different.

30. A compound according to claim 1, of formula (XXIIa):



or of formula (XXIIb):



where:

R^1 is $-CH_2NH_2$ or $-CH_2OH$, or a protected or derivatised version of such a group and R^4 is -H;

R^5 is -OH or a protected or derivatised version of such a group;

R^{14a} and R^{14b} are both -H or one is -H and the other is -OH or a protected or derivatised version of such a group, $-OCH_3$ or $-OCH_2CH_3$, or R^{14a} and R^{14b} together form a keto group;

R^{12} is $-NCH_3$-;

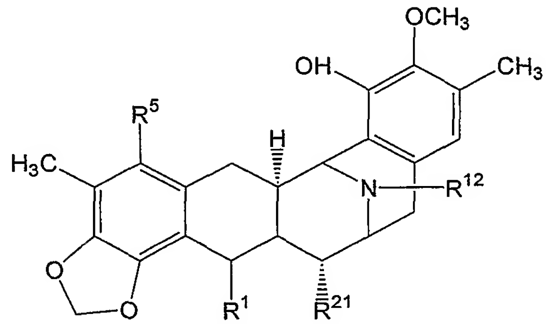
R^{15} is -OH or a protected or derivatised version of such a group; and

R^{18} is -OH or a protected or derivatised version of such a group.

31. A compound according to claim 30, wherein at least of R^1 , R^5, R^{14a}, R^{14b}, R^{15} or R^{18} is a protected or derivatised group.

32. A compound according to claim 30, wherein R^{14a} and R^{14b} are both -H.

33. A compound according to claim 1, of the general formula (XXIII):



where R^1 is a derivatised aminomethylene group of moderate bulk;

R^5 is a derivatised hydroxy group of low bulk;

R^{12} is $-NCH_3-$ and

R^{21} is a hydroxy or cyano group.

34. A compound according to claim 33, where R^1 is a hydrophobic group and lacks a free hydrophilic function.

35. A compound according to claim 33 or 34, wherein R^1 is a group $-CH_2-NH_2-CO-R^a$, where R^a has a linear chain length of less than 20 atoms.

36. A compound according to claim 33, 34 or 35 where R^5 is an acetyl group.

37. A compound according to any of claims 33 to 36, where the group R^1 is acylated on an $-NH_2$ group, and is an N-acyl derivative formed from a group $-CH_2NH_2$ or $-CH_2-NH-aa$.

38. A compound according to claim 37, where the acyl group is of formula $-CO-R^a$, where R^a is alkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, arylalkylene,

haloalkylarylakylene, acyl, haloacyl, arlyalkyl, alkenyl or amino acid.

39. A compound according to claim 33 or 34, where the group R^1 is a derivatised hydroxymethylene group.

40. A pharmaceutical composition comprising a comound according to any preceding claim, together with a pharmaceutically acceptable carrier.

41. The use of a compound according to any of claims 1 to 39, in the preparation of a pharmaceutical composition for use in the treatment of a tumour.

42. A method of treating a tumour, which comprises administering an effective amount of a compound according to any of claims 1 to 39.

INTERNATIONAL SEARCH REPORT

Interr Application No
PCT/GB 01/02110

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D515/22 C07D491/22 C07D471/18 A61K35/00
//(C07D515/22,317:00,291:00,241:00,221:00,221:00),(C07D491/22,
317:00,241:00,221:00,221:00),(C07D471/18,241:00,221:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E.J.COREY,DAVID Y.GIN, AND ROBERT S. KANIA: "Enantioselective Total Synthesis of Ecteinascidin" J.AM.CHEM.SOC., vol. 118, 1996, pages 9202-99203, XP002925428 page 203; table 1A	1
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X	examples 11,13	9,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 October 2001	24/10/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Goss, I

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/02110

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	J.W.LOWN, ALUMMOOTTIL V.JOSHUA ET AL.: "Molecular Mechanisms of Binding and Single-Strand Scission of Deoxyribonucleic Acid by the Antitumor Antibiotics saframycic A and C" BIOCHEMISTRY, vol. 21, no. 3, 1982, XP002925424 page 420; figure 1	1,2
X	RYUICHI SAKAI ET AL.: "Ecteinascidins: Putative Biosynthetic Precursors and Absolute Stereochemistry" J.AM.CHEM.SOC., vol. 118, 1996, pages 9017-9023, XP002925426 examples 12,13	1,2
X	US 5 721 362 A (COREY ELIAS J ET AL) 24 February 1998 (1998-02-24) cited in the application column 6; example 13	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 01/02110

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		CZ 9900914 A3	11-08-1999
		EP 0931083 A1	28-07-1999
		HU 0000068 A2	28-06-2000
		JP 2001501196 T	30-01-2001
		NO 991301 A	14-05-1999
		PL 332206 A1	30-08-1999
		WO 9812198 A1	26-03-1998